PEDIATRICS

PG Textbook of

PEDIATRICS

Volume **3**

Systemic Disorders
and Social Pediatrics

Piyush Gupta

PSN Menon

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Rakesh Lodha

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Volume 3

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PG Textbook of Pediatrics (Volume 3)

Dedicated to

*Children of India
and
Those Who Care for Them*

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Preface

In the last decade, many textbooks of pediatrics have been published in India. However, most were targeted towards undergraduates and general practitioners. The number of students opting for postgraduate courses in pediatrics is on the rise. Currently, most postgraduates in pediatrics augment their knowledge by reading and referencing to textbooks published abroad. Many of the Western textbooks are very detailed and provide an important amalgamation of clinical pediatrics with the major advances in genetics, genomics, physiology, diagnosis, imaging, and therapeutics. However, the "state-of-the-art" on the care of the normal and ill neonate, child, or adolescent as presented in these textbooks differ from that practiced in India or South Asia. While these books provide a detailed description of most disorders seen in children, they unfortunately do not provide both evidence-based medicine and astute personal clinical experiences from India. The focus is missing on the core issues relevant in the Indian context, i.e., growth, nutrition, immunization, development, newborn and adolescent health, and programmatic and social issues in child health. The need for a comprehensive postgraduate textbook, which can be adapted to Indian needs, has been recognized and expressed for some time now.

Rapid strides in medicine and technological advances in biological sciences were witnessed in the last decade. Advances in preventive and therapeutic care have opened new prospects for care of children. However, substantial improvements in quality of life have been limited to those with access to healthcare. Poverty, ignorance, war, bioterrorism, misplaced priorities and the lack of political will have prevented many children throughout the world, benefitting from these significant advances. Despite advances in infectious diseases, newer vaccines and preventive neonatal care, mortality and morbidity continue to be unacceptably high. Our priorities for care of children are often different from the developed world. Also, medical advances and good clinical practice must always be coupled with effective advocacy. These aspects need to be addressed in a postgraduate textbook, as current postgraduates are the future decision makers in our country.

It is our earnest wish and hope that the postgraduate textbook will help to fill the long-felt vacuum. It attempts to provide the essential information that postgraduates throughout India need to capture to effectively address the health problems that our children and youth may face in the times to come. Our objective is to be comprehensive yet concise and reader friendly, embracing both the new advances in science as well as the time-honored art of pediatric practice. Both Indian and international experts in respective fields have provided the details that have been further scrutinized for exposition and usefulness to pediatric postgraduates by a chosen team of eminent academicians. We have liberally included tables, line diagrams, images, clinical photographs, illustrative figures, flow charts and algorithms in the main text. The book is divided into 10 major Parts and further arranged into 51 Sections and Annexures to cover all aspects of postgraduate pediatric curriculum. Themes which have major public health relevance for India are extensively covered. It is almost impossible to cover all pediatric problems with the same degree of detail, and hence a careful balance has been made in the details of description of diseases and their management to the needs of the students, and to keep the book to a manageable size. Summary points "In A Nutshell" are provided at the end of each chapter. Selected recent references—mostly leading articles, reviews and position statements—are provided for more detailed information, if desired by the student or the teacher.

Some kind of overlap is unavoidable in a book of this magnitude, with 725 plus minds working on more than 600 chapters simultaneously. We have strived hard to minimize it. We have also tried our best to keep all the chapters on an even keel despite the unavoidable diversity of disciplines, thoughts, experience, and expressive capabilities of the distinguished authors and section editors, from all over the globe. The book would not have been possible but for the support that we received from these erudite contributors. We are indebted to them for their knowledge, introspection, and judgment during the entire process. Together we have worked hard to produce a compilation that will be helpful to those who desire to learn more about child health in India and thus provide better care for children.

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40.40 Preventive Cardiology in the Young

S Sivasankaran

42.11 Status Epilepticus

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42.24 Childhood Ataxia

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47.1 Common Visual Problems

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48.11 Cutaneous Manifestations of Collagen Vascular Diseases

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Section 41 — DISORDERS OF THE KIDNEY AND URINARY TRACT

Section Editors Arvind Bagga, Aditi Sinha

Chapter 41.1

Anatonmy and Physiology

M Vijayakumar, Arvind Bagga

ANATOMY

The two kidneys lie on either side of the vertebral column retroperitoneally on the posterior wall of the abdomen. They grow rapidly in the first year of life, from a birth length of 4.5 cm to an adult value of 11 cm. The outer 1–2 cm thick region of the kidney is called the cortex; the inner region is called the medulla with renal pyramids and the intervening renal columns constitute medulla. The base of the pyramids is at the corticomedullary border and the apices are the papillae, which project into minor calyces that join to form 3–4 major calyces and then the renal pelvis **(Fig. 1)**. The smooth muscle on walls of the calyces, pelvis and ureters contract to propel the urine toward the urinary bladder.

The main renal artery divides into five segments, which subsequently branch at the sides of the pyramids to form the interlobar artery, the arcuate artery, the interlobular artery and the afferent arteriole, which lead to glomerular capillaries. The efferent arteriole is formed by coming together of glomerular capillaries, which ultimately end in a secondary capillary network; the peritubular capillaries, which supply blood to the nephro . e venous system runs parallel to the arterial system, with interlobular,

arcuate, interlobar and renal veins. The lower splanchnic nerves give rise to sympathetic nervous fibers, which travel through the lumbar ganglion to the kidney. Renal blood flow is reduced by stimulation of the sympathetic nervous system due to intrarenal vasoconstriction. The renin-angiotensin aldosterone system is also stimulated by the sympathetic nervous system.

Nephrons

Nephrons are the functional unit of the kidney, each kidney having 1–1.2 million nephrons. Each nephron is composed of a glomerulus, proximal tubule loop of Henle, distal tubule and the collecting ducts **(Fig. 2** . e glomerulus filters blood, while providing a barrier to passage of protein and cells into the urine. The glomerulus consists of a network of capillaries supplied by the afferent arteriole and drained by the efferent arteriole. The endothelial cells of the glomerular capillaries are covered by the glomerular basement membrane and surrounded by foot processes of podocytes, constituting the filtration barrier. The fenestrated endothelium is freely permeable to water, small solutes and ost proteins, but is not permeable to the cellular components. Glycoproteins on the endothelial cells confer a negative charge, which prevents filtration of negatively charged proteins. The endothelial cells also produce vasoactive substances, such as angiotensin, prostaglandins, nitric acid, endothelin-1,

Figure 1 Longitudinal section of the kidney
Source: Reproduced with permission from Vijayakumar M, Nammalwar BR. Principles and Practice of Pediatric Nephrology. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2013.
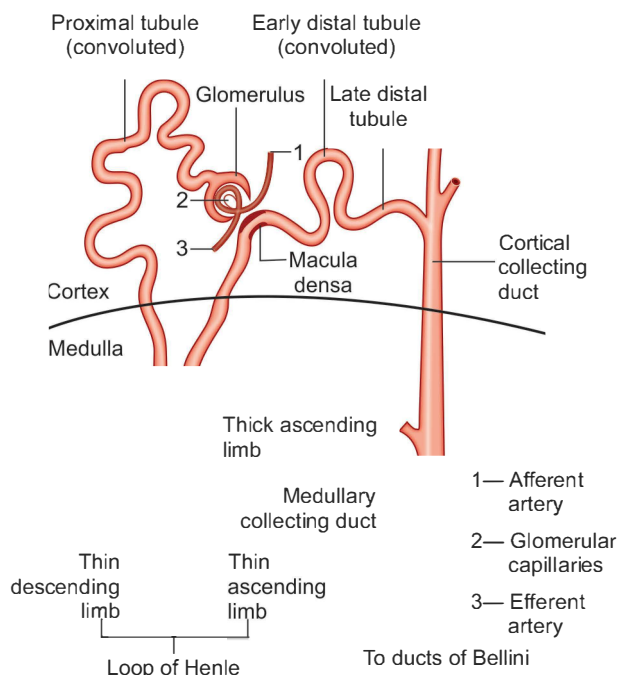
Figure 2 Diagrammatic representation of the nephron
Source: Reproduced with permission from: Vijayakumar M, Nammalwar BR. Principles and Practice of Pediatric Nephrology. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2013.

bradykinins and glucocorticoids which are important in controlling renal blood flow. The basement membrane, a porous matrix of negatively charged proteins including type IV collagen, laminin, proteoglycans and fibronectin, is an important barrier to plasma proteins. Podocytes have foot processes that interdigitate to cover the basement membrane and are separated by filtration slits. These slits are bridged by a porous diaphragm composed of several proteins including nephrin, podocin, actinin 4 and CD2AP.

Glomeruli of the superficial nephrons are located in the outer cortex; their loop of Henle is short and its efferent arteriole branches into peritubular capillaries that surround the nephron segments of its own and adjacent nephrons. This capillary network enables delivery of substances to the nephron for secretion and return of reabsorbed water and solutes to the circulation. At the corticomedullary junction are the juxtamedullary nephrons, which have a long loops of Henle extending deep into the medulla. The efferent arteriole forms both a network of peritubular capillaries and also number of vascular loops called the vasa recta deep in the medulla. The long loops of Henle and its vasa recta serve to concentrate and dilute the urine.

Juxtaglomerular Apparatus

The juxtaglomerular apparatus is composed of thickened epithelial cells of the afferent arteriole (granular cells), specialized cells lining the wall of the distal tubule (macula densa) and the extraglomerular mesangial cells. Activation of rennin-angiotensin-aldosterone and sodium conservation takes place through the juxtaglomerular apparatus.

The glomerular filtrate enters the tubule as tubular fluid wherein reabsorption and secretion of solutes, electrolytes and water occurs along with some amount of diffusion to adjust the urinary composition and maintain the homeostasis of body fluid. Each nephron segment has specific transport functions. Almost all cells in the nephron have a single nonmotile primary cilium, which protrudes into the tubular fluid. Primary cilia act as mechanosensors that sense changes in flow rate of the tubular fluid, and chemosensors that sense or respond to compounds in the surrounding fluids and initiate calcium dependent signaling pathways including those that control kidney cell function, proliferation, differentiation and apoptosis. The process of reabsorption of solutes, electrolytes and water from the tubular fluid to blood across the renal tubular cell membrane and secretion from the peritubular capillary blood to tubular fluid is the result of specialized membrane carrier proteins called transporters, through specialized channels or by diffusion. Active transporters are Na^+/K^+ ATPase, Ca^{2+} ATPase, H^+/K^+ ATPase and H^+ ATPase. The passive transporters are the cotransporters (e.g., $Na^+/K^+/Cl^-$ and Na^+ glucose) and exchangers (Ca^+/Na^+ and H^+/Na^+).

PHYSIOLOGY

Functions of the Nephron

The followings are essential functions of the nephron:
1. Regulation of osmolality through excretion of osmotically dilute or concentrated urine.
2. Regulation of concentration of numerous ions in blood and plasma like Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, HCO_3^-, phosphate and sulfate.
3. Regulation of acid base balance through excretion of H^+ when there is excess acid, or HCO_3^- when there is excess base, maintaining the acid base status.
4. Regulation of extracellular fluid volume by controlling excretion of Na^+ and water.
5. Regulation of blood pressure by modifying urinary Na^+ excretion and secreting various substances like renin, which modulate blood pressure.

6. Elimination of metabolic waste products like urea, the main nitrogen containing product of protein metabolism, uric acid, the end product of purine metabolism, and creatinine, the end product of muscle degradation.
7. Elimination of drugs and toxic compounds.
8. Production of hormones like erythropoietin and $1,25(OH)_2$ vitamin D3 that are important in maintaining hemoglobin concentration and bone health.
9. Degradation of polypeptide hormones like insulin, glucagon, and parathormone.
10. Ammonia synthesis, which plays a vital role in acid base balance.
11. Synthesis of substances affecting renal blood flow and Na^+ excretion: arachidonic acid derivatives, prostaglandins, thromboxane A2 and kallikrein.

Specific Functions

The modulations in afferent and efferent arteriolar tone affect the intracapillary pressure which in turn intrinsically regulates the glomerular filtration rate (GFR). The GFR is maintained at constant level over a wide range of blood pressure by the process of autoregulation. In the proximal tubules isonatremic reabsorption of tubular fluid occurs, where sodium and water reabsorption is predominant. The thick ascending limb of loop of Henle is a diluting segment where sodium chloride is increasingly reabsorbed but not water. The distal nephron, derived from the original ureteric bud, responds to hormones that regulate volume osmolality and potassium concentration. The junction between the diluting and concentrating segments at the juxtaglomerular apparatus is the point where tubular functions decide the rate of glomerular filtration.

Seventy to eighty percent of the filtered salt and water is reabsorbed at the proximal tubule **(Fig. 3)**. This is an active process and the energy is derived from Na^+-K^+-ATPase pump. Water and sodium reabsorption at this site is aided by hyperoncotic peritubular capillary fluid. Cotransport of glucose, phosphate and amino acids are important at this site. Hydrogen secretion by the proximal epithelial cell is important for reabsorption of filtered bicarbonate **(Fig. 4)**. Carbonic anhydrase is important for this function in addition to the sodium gradient. If sodium gradient fails due to dysfunction, as in Fanconi syndrome, proximal tubular reabsorption of bicarbonate, glucose, phosphate and amino acids are impaired.

Sodium is actively pumped into renal interstitium from the thick ascending limb of Henle. Water cannot go along with sodium due to water proofing effect of Tamm Horsfall proteins secreted at this site. The tubular fluid osmolality is less than 80 mOsm/kg but interstitium becomes hyperosmolar with 1,400 mOsm/kg tonicity at the renal papillae, which is essential for subsequent water reabsorption from the collecting ducts. Tubuloglomerular feedback at the juxtaglomerular region is the process that regulates tubular and hence glomerular function at this point of the tubule. At this site, the specialized tubular cells of the macula densa relate closely with the juxtaglomerular apparatus and also the afferent and efferent arterioles.

Distal convoluted tubule (DCT) is very important for the fine tuning of the acid-base regulation of the body and for reabsorption and secretion of salts **(Fig. 5)**. Three types of cells are present here. Principal cells of the DCT regulate potassium secretion into and sodium reabsorption from the urine and are dependent on aldosterone as well as on the delivery of sodium to the lumen of the DCT to be exchanged with potassium. The epithelial sodium channels (ENaCs), which are located on the apical aspects of the cell, are essential for the rate-limiting step for sodium recovery and are synthesized in response to aldosterone. The second important cell is the intercalated cell which regulates the secretion of hydrogen ions into the urine in exchange for potassium. The final cell type is
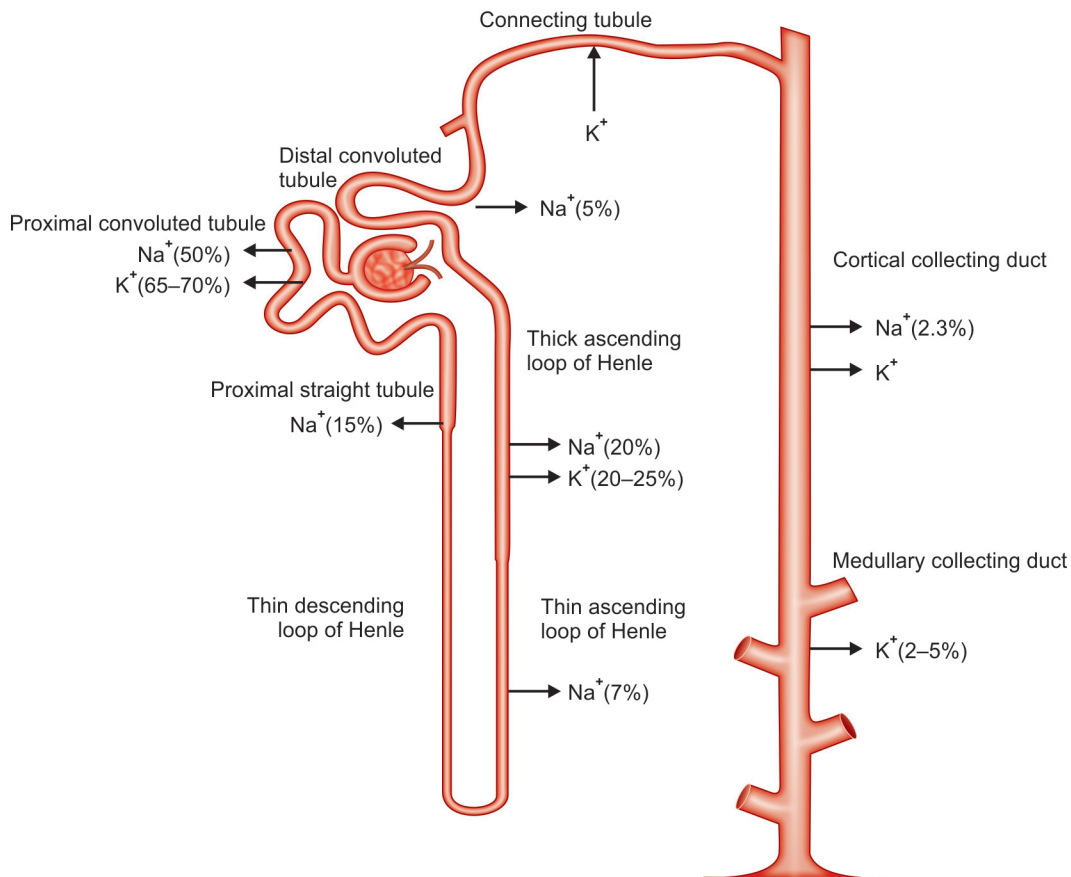
Figure 3 Renal tubular handling of sodium and potassium. The major sites of reabsorption are shown, with percentage of filtered cation in parenthesis
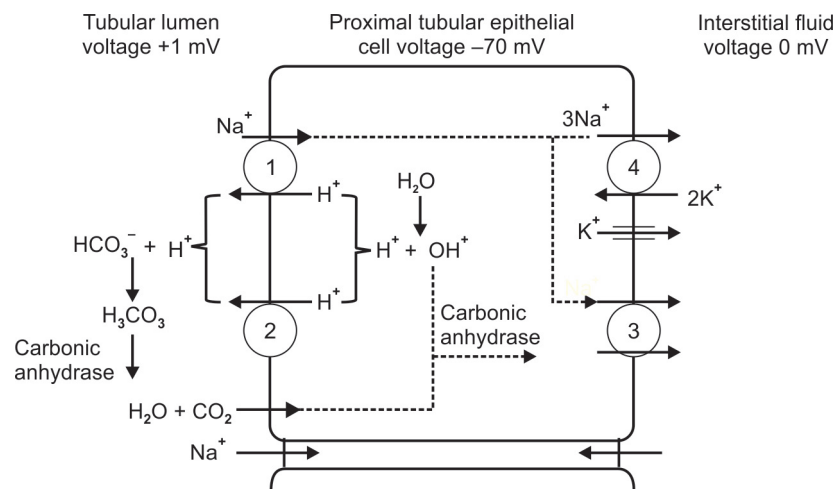
Figure 4 Reabsorption of bicarbonate in the proximal tubule. Protons (H^+), secreted into the lumen through the sodium (Na^+) H^+ antiporter (1) and H^+ ATPase (2), combines with HCO_3^- to form H_2CO_3 that under the action of luminal membrane carbonic anhydrase dissociates to H_2O and CO_2. The CO_2 travels across the membrane into the cell where it combines with OH^- to generate HCO_3^-. The HCO_3^- and Na^+ cross the basolateral membrane using the Na^+/HCO_3^- symporter (3). Na^+ also exits the cell via the Na^+/K^+ ATPase (4). Electrogenic H^+ secretion generates a small lumen positive voltage, which creates current flow across the paracellular pathway

sodium chloride cotransporter, which are inhibited by thiazides. This cell is important in the reabsorption of calcium from the urine.

Healthy children on salt restriction can reabsorb 99% of the sodium from the nephron with only 1% being excreted. In preterm infants, 5% of the filtered sodium is excreted. Renin angiotensin system is not the only stimulus for aldosterone.

Hyperkalemia can also stimulate aldosterone secretion, thereby controlling its urinary excretion. Collecting ducts, derived from the ureteric bud, are responsible for reabsorption of water through the action of vasopressin on water permeable channels called aquaporins. Aquaporins, especially aquaporin 2, rapidly move from intracytoplasmic vesicles into the plasma membrane

Intercalated cell

Principal cell

Tubular lumen voltage −10 mV

Voltage −30 mV

Interstitial fluid voltage 0 mV

Voltage −80 mV
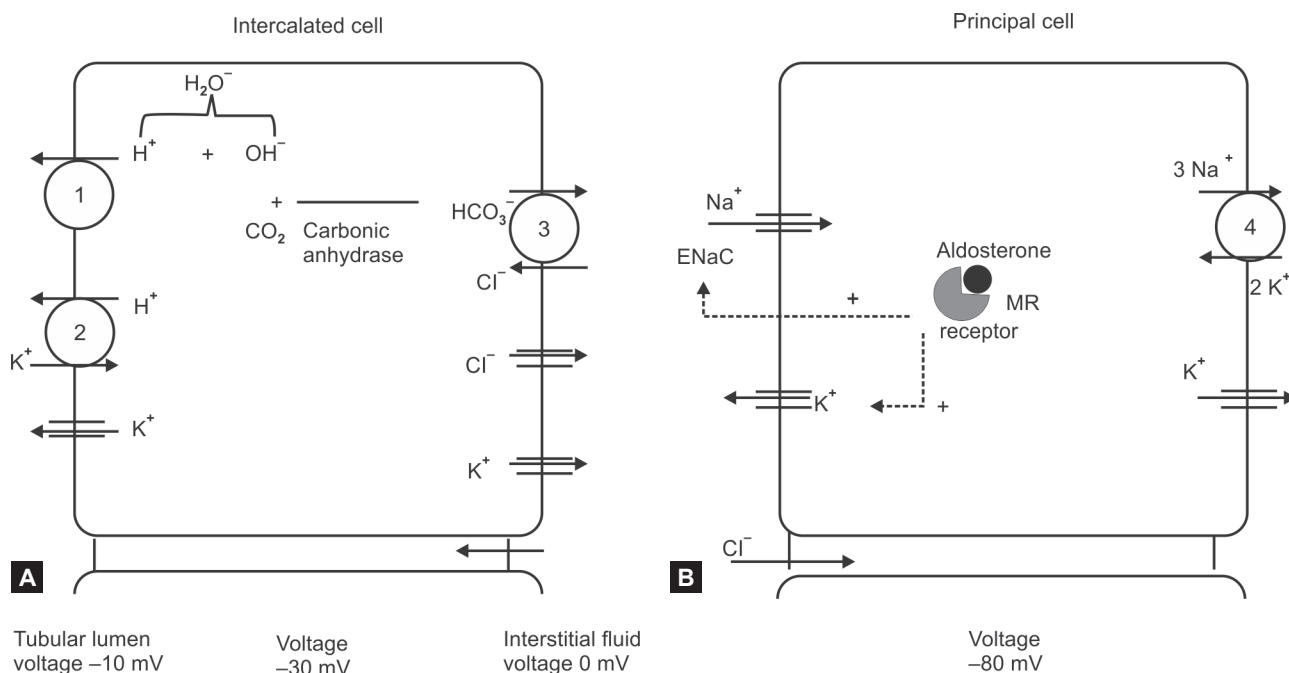
Figures 5A and B Mechanism of acidification and potassium excretion in the distal renal tubules. (A) The intercalated cells of the cortical collecting ducts secrete H^+ through the H^+ ATPase (1) and H^+/K^+ ATPase (2), independent of Na^+ transport. The hydroxyl (OH^-) ions generated in the cell through H^+ secretion exit the cell by the HCO_3^-/Cl^- exchanger (3). The secreted H^+ is buffered by luminal ammonia forming NH_4^+ and phosphate (titratable acids), to prevent a drop in luminal pH that would prevent further H^+ secretion; (B) Principal cells mediate sodium (Na^+) absorption and potassium (K^+) transport. The apical membrane contains an amiloride sensitive Na^+ channel (ENaC); Na^+ exits basolaterally *via* Na^+/K^+ ATPase (4). Sodium transport creates a lumen negative transepithelial potential that increases the rate of H^+ secretion by intercalated cells. Aldosterone binds to the mineralocorticoid (MR) receptor and enhances Na^+ absorption and H^+ and K^+ secretion

of the collecting ducts in response to vasopressin. Binding of vasopressin to vasopressin receptors leads to activation of adenylyl cyclase, which increases intracellular cyclic AMP. Thereafter activation of cAMP-dependent protein kinase A mediates protein phosphorylation, which triggers exocytic insertion of AQP2 channels into the apical membrane. These channels increase water permeability of the apical membrane, facilitating water transport. Water moves down an osmotic gradient from the dilute urine arriving in the distal nephron to the hyperosmolar medullary interstitium surrounding the collecting ducts. The maximum urine concentration capacity depends on the presence of vasopressin, the integrity of vasopressin 2 receptors and aquaporin assembly, and high concentration of medullary interstitial solute constituted chiefly by sodium and urea.

MORE ON THIS TOPIC

Bagga A, Gulati A. Renal anatomy and physiology. In: Srivastava RN, Bagga A. Pediatric Nephrology. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2011. pp. 1-19.

Davis ID, Avner ED. Glomerular diseases. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Saunders; 2011. pp. 1730-1.

Eaton DC, Pooler JP. Renal functions, basic processes and anatomy. In: Eaton DC, Pooler JP. Vander's Renal Physiology. 7th ed. New York: McGraw Hill; 2009. pp. 1-19.

Koepen BM, Stanton BA. Structure and Function of the Kidneys in Renal Physiology. 4th ed. Philadelphia: Mosby; 2009. pp. 19-30.

Nammalwar BR, Vijayakumar M. Structure and functions of the kidney. In: Vijayakumar M, Nammalwar BR. Principles and Practice of Pediatric Nephrology. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2013. pp. 3-9.

Saleem MA, Tizard J, Dudley J, et al. Disorders of the urinary system. In: McIntosh N, Helms P, Smyth R, Logan S. Forfar and Arneil's Textbook of Pediatrics, 7th ed. London: Churchill Livingstone; 2008. pp. 545-99.

IN A NUTSHELL

1. Glomerular capillary hydrostatic pressure generates a protein-free filtrate of plasma into Bowman's capsule, with the glomerular filtration rate determined by relative constriction of afferent and efferent arterioles.
2. The proximal tubules reabsorb 65% of the filtrate.
3. The impermeability of the thick ascending limb in Henle's loop is responsible for medullary interstitial hypertonicity, which is important for urinary concentration.
4. The distal tubule is involved in aldosterone controlled sodium reabsorption and Na^+/K^+ exchange.
5. Cells of the distal tubule and collecting ducts secrete H^+ ions leading to maximum urine acidification.
6. Water is reabsorbed in the collecting ducts in response to ADH collecting ducts in response to ADH.

Chapter 41.2
Investigations for Kidneys and Urinary Tract
Susan Uthup, Jyoti Sharma

URINE EXAMINATION

Urinalysis is a simple, quick and inexpensive investigation. Urine specimens should be fresh and clean-voided midstream in older children.

Urine Macroscopic Examination

Depending on the concentration of urine, its color varies from pale yellow to amber. Red or tea-color urine suggests the presence of blood, hemoglobin, myoglobin, porphyrin, or nonpathologic pigments (beets, food color or medication). Blue to green suggests the presence of biliverdin or *Pseudomonas* infection. Urine is normally clear, but can be turbid in the presence of leukocytes, epithelial cells, bacteria, or crystals.

Dipsticks are commercially available, chemically impregnated reagent strips that employ a colorimetric change for pH, specific gravity, protein, blood, glucose, ketone, leukocytes, and nitrites in the urine. The strip should not be dipped for more than a few seconds in the urine; excess urine should be blotted off on the edge of absorbent paper to prevent mixing of reagents and the specific tests should be read at the appropriate time.

Specific gravity ranges from 1,001–1,035 and may be measured by a dipstick, refractometer or a urinometer. It reflects the concentrating and diluting ability of the kidney and under normal conditions, the hydration status. A low specific gravity is seen in polydipsia and diabetes insipidus; in a dehydrated child, a low value (< 1,007) represents a concentrating defect. When the kidneys can neither dilute nor concentrate the urine, specific gravity becomes fixed at 1,010 (isosthenuria).

Urinary pH can be estimated from a fresh urine specimen using a reagent test strip or a pH meter; it usually ranges from 5.0 to 8.0. Estimation of urinary pH is important in diagnosing renal tubular acidosis. Therapeutic urinary alkalinization is recommended in the management of uric acid and cystine stones, and management of certain poisonings (salicylates, barbiturate and methotrexate), rhabdomyolysis and tumor lysis syndrome.

Hemoglobin Urine dipsticks are sensitive to urine red cells, free hemoglobin and myoglobin.

Glucose is not usually present in the urine. Glucosuria can occur when there is hyperglycemia (plasma glucose concentration > 180–200 mg/dL) or reflect a defect in proximal tubule cells to reabsorb a normal filtered glucose load. Glucosuria without hyperglycemia may occur as an isolated defect due to a mutation in the SGLT2 transporter or, more commonly, as part of a generalized proximal tubule cell dysfunction (phosphaturia, aminoaciduria and bicarbonate wasting) referred to as Fanconi syndrome. Reagent test strips impregnated with glucose oxidase only detect glucose. Other sugars, such as galactose, lactose, fructose and mannose, can be detected by the Benedict test.

Nitrite and leukocyte esterase: Escherichia coli, Enterobacter, Citrobacter, Klebsiella, and *Proteus* species are able to reduce dietary nitrate to nitrite. Positive nitrites in the urine are strongly suggestive of the presence of a significant number of bacteria, and a urine culture should be performed. Because bacteria require 4 hours to convert nitrate to nitrite, a false negative can occur if the urine has not been present in the urinary tract for sufficient time. Dipsticks detect leukocyte esterase, an enzyme found in neutrophils, and a positive test suggests the presence of leukocyturia.

Urine Microscopic Examination

Approximately 10 mL fresh urine is centrifuged for 5 min, the supernatant decanted, and the remaining drop examined on a clean slide for presence of casts, cells, crystals and bacteria.

Red blood cells Hematuria is defined as the presence of more than five red blood cells (RBCs) per high power field in a centrifuged urine or positive dipstick test for blood. In a patient who has urine that appears grossly bloody, a strongly positive dipstick with minimal RBCs visualized on microscopy suggests presence of myoglobin (rhabdomyolysis) or hemoglobin (intravascular hemolysis). Urine microscopy is useful in determining the etiology of hematuria since presence of dysmorphic RBCs (RBCs with membrane blebs, an irregular surface) and RBC casts suggests a glomerular disease.

White blood cells Greater than five white blood cells per high-power field is considered abnormal. Neutrophils in urine may be due to UTI, proliferative glomerulonephritis (GN), interstitial nephritis calculi or fever. Epithelial cells, i.e., renal tubular cells, transitional cells, and squamous epithelial cells may be observed in normal urine. Increased numbers of renal tubular cells may be seen with acute tubular injury (acute tubular necrosis, acute transplant rejection, and exposure to nephrotoxic agents).

Bacteria in the urine sediment in an asymptomatic child are most likely due to contamination with normal flora from the external urethral meatus or vagina. When seen in an unspun fresh sample, the presence of bacteria is highly suggestive of significant bacteriuria.

Casts are best seen in freshly voided unspun urine as cellular casts can dissolve within 30 min in acidic urine, within 10 min in alkaline dilute urine and centrifugation may damage them. They are formed in the lumen of distal convoluted tubules and collecting ducts and consist of an organic matrix composed of Tamm-Horsfall mucoprotein with or without cellular elements. Hyaline casts are common and can be seen in normal individuals and in proteinuric states. They may appear waxy if lipid droplets are present. Granular casts consist of proteins and degenerated tubular cells and may be seen in GN, pyelonephritis, strenuous exercise, fever and malignant hypertension. RBC casts are pathognomonic of glomerular disease and leukocyte casts can be seen with pyelonephritis, interstitial nephritis or postinfectious GN.

Crystals appear after the urine stands for a period. Uric acid and calcium oxalate crystals may be seen in normal conditions; cystine crystals are seen in cystinuria. Sulfadiazine, aciclovir, indinavir, vitamin C and amoxicillin may cause crystal formation when high doses are used and there is concomitant dehydration. Calcium carbonate and amorphous phosphate and amorphous urates are of no clinical significance.

Urinary protein excretion Normally Tamm-Horsfall proteins are secreted by tubular cells of thick ascending limb of Henle. In glomerular disease, large amounts of albumin are lost.

ASSESSMENT OF GLOMERULAR FILTRATION

Blood urea is the primary metabolite derived from dietary protein and tissue protein turnover. Blood urea nitrogen is roughly one-half of the blood urea level (normal 20–40 mg/dL); the urea: creatinine ratio is 20–40:1. Disproportionate rise in blood urea compared to serum creatinine are seen in dehydration, upper gastrointestinal bleed, hypercatabolic states like sepsis, burns, crush injuries and in patients on steroids. Low urea levels are seen in starvation, low protein intake and severe liver disease.

Glomerular filtration rate (GFR) is the most commonly used measure of kidney function. Inulin clearance is considered the gold standard for measuring GFR, but is cumbersome to perform. Creatinine clearance (CrCl) measurement is widely used and correlates well with inulin clearance within the normal range of GFR; however, calculation requires timed urine collection. For practical purposes, plasma concentration of endogenously produced creatinine or cystatin C is used for estimation of GFR. The modified Schwartz formula is used for estimation of GFR.

GFR (mL/min/1.73 m^2) = k × height (cm) ÷ serum creatinine, where k = 0.41 in children 1–16 years old.

GFR is low in infancy and reaches normal adult level (118 ± 18 mL/min/1.73 m^2) by 2 years of age.

Cystatin C is a low molecular weight protein (13.36 KDa) produced by all nucleated cells with a stable production rate. Estimated by enzyme immunoassays or immunoturbidometry, this protein is influenced less by age, gender, and muscle mass than creatinine, and correlates better with GFR. Formulae have been proposed that provide an estimate of GFR.

ASSESSMENT OF TUBULAR FUNCTION

Plasma ultrafiltrate from the glomerulus enters the proximal tubule where 60–65% is reabsorbed. In disorders of the proximal tubule, excessive amounts of the solutes will be found in the urine. The fractional excretion of sodium and tubular reabsorption of phosphate is used to assess the integrity of the proximal tubules. Detection of glucosuria and aminoaciduria are indicative of proximal tubular disorder **(Table 1)**.

HISTOPATHOLOGICAL EVALUATION

Renal histopathology forms an integral part of diagnosis of certain renal disorders, e.g., crescentic GN and IgA nephropathy. The procedure is important for diagnosis and prognostication (e.g., steroid resistant nephrotic syndrome) and for planning management (e.g., steroid resistance, lupus nephritis). Under aseptic precautions, 2–3 cores of renal cortex are obtained with an 18-gauge needle. The sample is subjected to light microscopy, immunofluorescence and when indicated, electron microscopy.

IMAGING OF THE KIDNEYS AND URINARY TRACT

Ultrasonography

Ultrasound of kidneys, ureters and bladder is the most common initial imaging tool for evaluation of kidney diseases. The procedure is safe, easy to perform, noninvasive, painless, and relatively inexpensive. Renal location, contour, size, corticomedullary differentiation as well as the status of collecting system and bladder can be assessed easily **(Fig. 1)**. Repeated studies can be performed without the risk of radiation or contrast. However, the procedure is operator dependent, difficult to interpret and functional assessment is not possible. Renal vascularity and perfusion can be assessed by color Doppler. Antenatal ultrasound is a perfect screening tool for detection of renal anomalies including dysplastic kidney, hydronephrosis and posterior urethral valves. Ultrasound is used for evaluation of patients with congenital abnormalities of the kidney and urinary tract **(Fig. 2)**, urinary tract infection, hematuria, proteinuria, renal stones, abdominal mass, acute kidney injury and chronic kidney disease. The presence of small contracted echogenic kidneys with loss of corticomedullary differentiation points to diagnosis of chronic kidney disease. Renal biopsy and catheter drainage of the dilated urinary tract can be done under ultrasound guidance.

Plain X-ray

A plain radiograph of abdomen delineates the kidneys and urinary tract. A radiolucent halo outlined by perinephric fat outlines the kidneys. Radiopaque renal, ureteric or bladder calculi, vertebral anomaly, indwelling catheters and stents can be seen. Conventional X-ray can show skeletal abnormalities of mineral bone disease.

Figure 1 Ultrasound of a normal child's kidney showing hyperechoic medulla with sinus complex and hypoechoic cortex. The echogenicity is compared to the adjacent liver

Table 1 Assessment of tubular function

Test	Estimation/Formula	Interpretation
Fractional excretion of sodium (FENa)	$\dfrac{\text{Urinary sodium} \times \text{plasma creatinine}}{\text{Plasma sodium} \times \text{urinary creatinine}} \times 100$	Prerenal failure: FENa < 1% in children; < 2.5% in neonates Acute tubular necrosis: FENa > 2% in children; > 2.5% in neonates
Tubular reabsorption of phosphate %	$1 - \dfrac{(\text{Urinary phosphate} \times \text{plasma creatinine})}{(\text{Plasma phosphate} \times \text{urinary creatinine})} \times 100$	TRP < 85% indicates urinary phosphate wasting
Transtubular potassium gradient	$\dfrac{\text{Urinary potassium} \times \text{plasma osmolality}}{\text{Plasma potassium} \times \text{urinary osmolality}}$	Urinary sodium should be > 25 mEq/L and urine osmolality should be greater than plasma osmolality Hypokalemia: TTKG > 2.5 indicates renal potassium wasting Hyperkalemia: TTKG < 5 indicates hypoaldosteronism
Calcium excretion	24 hours urinary calcium	Normal < 4 mg/kg/day; < 0.1 mmol/kg/day
	Calcium/Creatinine ratio in spot urine specimen	Normal < 0.5 in neonates and infants; < 0.2 in older children
Chloride excretion	Estimated in random urine sample	Metabolic alkalosis: Urinary chloride > 10 mEq/L suggests renal chloride loss; < 10 mEq/L suggests gastrointestinal loss or volume contraction
Urine anion gap	Urinary sodium + potassium – chloride	Positive urinary anion gap in a patient with normal anion gap metabolic acidosis suggests renal tubular acidosis

Figure 2 Ultrasound showing hydronephrosis in a neonate. See the enlarged dilated renal pelvis and calyces

Figure 3 Voiding cystourethrography showing bilateral grade 4 vesicoureteric reflux in a child with recurrent urinary infections
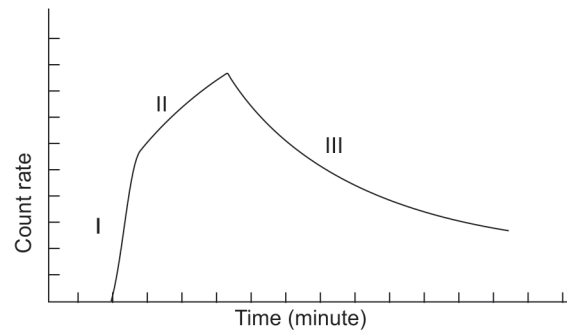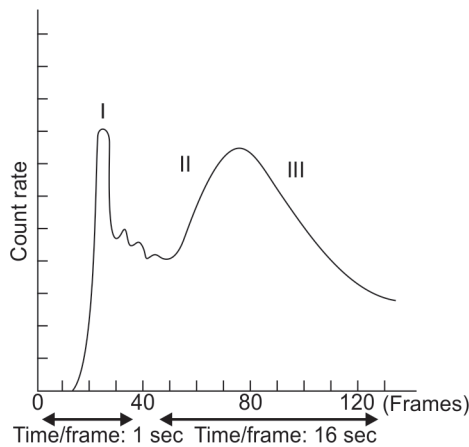
Figure 4 Normal dynamic renal scintigraphy using DTPA. Note the first pass perfusion and function curves

Intravenous Urography

Intravenous urography (IVU) is excellent in giving anatomic details, but entails radiation exposure and use of contrast medium (urografin 3–4 mL/kg). Initial scout film of the IVU shows radiopaque stones and the bowel gas pattern. The renogram phase shows contrast uptake by renal parenchyma. Frontal films at 3 min and 15 min evaluate the upper urinary tract. Delayed films, at 24 hours, show fullness of the obstructed renal unit.

Voiding Cystourethrography

Voiding cystourethrography (VCUG) or micturating cystourethrography (MCU) helps to assess lower urinary tract. This is indicated in evaluation of antenatal hydronephrosis, urinary tract infections, suspected obstructive anomaly, voiding dysfunction and neurogenic bladder. It is used in diagnosis and grading of vesicoureteric reflux. Urinary tract infection should be ruled out prior to the procedure. Prophylactic antibiotic should be given 30 min before and 6 hours after the procedure. Bladder is catheterized and slowly filled with diluted contrast medium (volume based on bladder capacity). Assessment is done during the filling phase, with full bladder, voiding and after emptying **(Fig. 3)**. *Radionuclide cystography* is satisfactory for follow-up studies in patients with reflux since the radiation exposure is lower.

Computerized Tomography

Excellent anatomical details are obtained on computerized tomography (CT) scan. Radiation exposure, contrast toxicity and need for sedation are the limiting factors. CT scan is useful for evaluation of abdominal trauma, renal injury, intrarenal infections (renal abscess and perinephric collections) and renal tumors.

Renal Scintigraphy

Radionuclide scintigraphy helps to assess renal blood flow, global and single kidney GFR, renal structure and presence of scars. It is highly sensitive, noninvasive and uses less radiation compared to IVU and CT scan.

Renography Tc-labelled radiopharmaceutical is injected IV and its uptake and elimination by the kidney is monitored. Glomerular filtration agent, diethylenetriaminepentaacetate (DTPA), is used commonly. Three phases are described for quantifying the renogram. These include perfusion phase (0–30 s) representing first passage of the radioactive bolus into the kidney, parenchymal phase (40–160 s) representing glomerular filtration and the excretory phase (3–20 min) **(Fig. 4)**. The differential function of each kidney can be derived by the area or slope of the renal time activity curve. Furosemide renography is used in the evaluation of
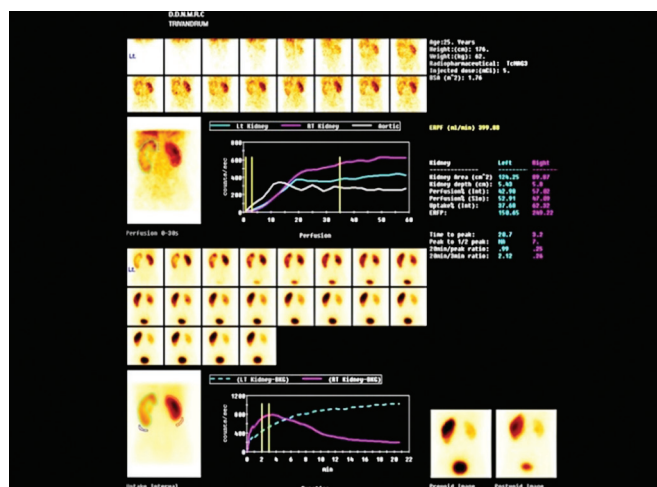
Figure 5 Furosemide renography showing obstructed flow pattern in the left kidney
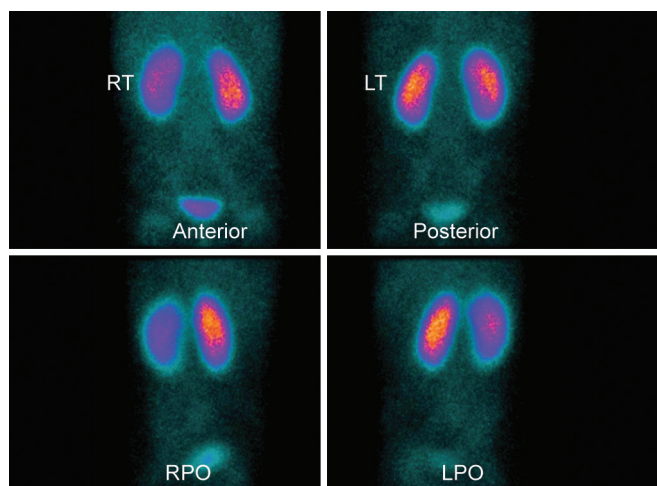
Figure 6 Static renography using DMSA showing areas of cortical uptake by normal kidneys

obstruction **(Fig. 5)**. Captopril renogram is used for evaluation of renovascular hypertension.

Renal static imaging Dimercaptosuccinic acid (DMSA) is concentrated in the renal tubules and gives excellent images of the cortex **(Fig. 6)**. It is useful to define areas of inflammation and is the reference investigation for detection of renal cortical scarring.

Magnetic Resonance Urography

Magnetic resonance urography gives both anatomic and functional information. It correlates well with furosemide renal scan and may be superior in terms of determining nonobstructive from obstructive hydronephrosis. The need for sedation, cost and need for specialized protocols limit the use of the investigation in children. Patients with reduced renal function may be at risk of nephrogenic systemic fibrosis with the use of gadolinium contrast.

MORE ON THIS TOPIC

Bagga A, Sinha A, Gulati A. Protocols in Pediatric Nephrology. New Delhi: CBS; 2012.

Friedman A. Laboratory assessment and investigation of renal function. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N. Pediatric Nephrology. 6th ed. Berlin Heidelberg: Springer-Verlag; 2009. pp. 491-504.

Goodyer P, Phadke K. Evaluation of renal diseases. In: Phadke K, Goodyer P, Bitzan M. Manual of Pediatric Nephrology. Berlin Heidelberg: Springer; 2014. pp. 1-64.

John RS, Cynthia GP. Genitourinary imaging techniques. Pediatr Clin N Am. 2006;53:339-61.

Langlois V. Laboratory evaluation at different ages. Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008. pp. 39-54.

Reddy PP. Recent advances in pediatric uroradiology. Indian J Urol. 2007;23:392-402.

Sharma J, Vasudevan A. Appendix. In: Phadke K, Goodyer P, Bitzan M. Manual of Pediatric Nephrology. Berlin Heidelberg: Springer; 2014. pp. 516-50.

Simoneaux SF, Greenbaum LA. Diagnostic imaging. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N. Pediatric Nephrology. USA: Lippincott Williams Wilkins; 2009. pp. 535-64.

Srivastava RN. Diagnostic evaluation of kidney and urinary tract. In: Parthasarathy A, Menon PSN, Gupta P, Nair MKC. IAP Textbook of Pediatrics. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2013. pp. 606-11.

IN A NUTSHELL

1. A carefully performed urinalysis on a fresh urine sample provides a great deal of information toward the diagnosis of renal disorders, while dipsticks are useful screening tools.
2. Estimation of GFR continues to rely on serum creatinine; Cystatin C is a similar molecule that rises early in acute kidney injury and correlates better with GFR.
3. Choice of tubular function tests should be tailored to the suspected disease.
4. Ultrasound of kidneys, ureters and bladder is the most common initial imaging tool.
5. Specific tests for imaging and radionuclide scans should be chosen judiciously depending on the information required.

Chapter 41.3
Congenital Anomalies of Kidneys and Urinary Tract
Shilpa Sharma, Aditi Sinha

Congenital anomalies of the kidney and urinary tract (CAKUT) result from abnormal embryonic development of the renal parenchyma or the developing collecting system or abnormalities in renal migration. While certain abnormalities require early evaluation and management, in others parental anxiety should be allayed and appropriate follow-up advised.

EPIDEMIOLOGY

Congenital anomalies of the kidney and urinary tract may be diagnosed during the prenatal period, in the neonatal age or during later childhood. These constitute approximately 20–30% of anomalies identified on antenatal ultrasound. Their incidence in live and stillborn infants is 0.3–1.6 per 1,000. However, it is not unusual for CAKUT to present in late childhood with urinary tract infections, abdominal lump or end stage renal disease.

PELVIURETERIC JUNCTION OBSTRUCTION

Hydronephrosis, or dilatation of the pelvicalyceal system, is commonly caused by functional or mechanical obstruction at the pelviureteric junction (PUJ). The obstruction may be discovered on prenatal ultrasound or present later in childhood with abdominal lump with or without dysfunction of the affected kidney.

Etiology

Pelviureteric junction obstruction may develop due to (1) an intrinsic defect (e.g., muscular deficiency at the PUJ, high insertion of ureter into pelvis, persistent ureteral folds, ureteral stenosis or hypoplasia, or angulation and adhesions at PUJ), (2) intraluminal obstruction (e.g., polyp, papilloma or valves), or (3) extraluminal compression (e.g., by aberrant vessels crossing over the ureter). In an unobstructed system, urine flows from the renal pelvis into the ureters by anatomical continuity and peristaltic contractions of the pelvis and ureter. Obstruction to flow causes rise in pelvic pressure from the baseline (5–25 cm water), pelvic dilatation and parenchymal injury.

Clinical Features

While a majority of cases are picked up on antenatal ultrasonography, PUJ obstruction may sometimes be detected incidentally on abdominal ultrasound. Most children with congenital PUJ obstruction remain asymptomatic throughout life. However, depending on the degree and duration of obstruction, they may present with: (1) renal lump, (2) flank pain, (3) urinary tract infection, (4) stone (due to stasis and/or infection), (5) Dietl crisis (an acute presentation with flank lump, nausea and vomiting relieved by passage of large amount of urine), or (6) hematuria (rare, usually after trauma). Renal failure is unlikely unless PUJ obstruction affects a solitary kidney or is bilateral.

Course

Over 50–70% cases of unilateral hydronephrosis detected on antenatal ultrasound are transient, resolving completely during follow-up without loss of renal function. Renal function remains stable in 20–30% of cases despite persisting hydronephrosis due to PUJ obstruction. Since renal function deteriorates in the remaining 10% of cases with significant PUJ obstruction, a close follow-up is essential, especially during the first 2 years to identify the subgroup of patients that requires surgery. About 5–10% cases of PUJ obstruction may have associated vesicoureteric reflux (VUR), unilaterally or bilaterally, requiring evaluation.

Investigations

The evaluation for antenatally detected hydronephrosis is summarized at the end of the chapter. Investigations in patients with suspected PUJ obstruction include estimation of blood levels of urea, creatinine and electrolytes, and urinalysis. Being noninvasive, *ultrasonography* is the preferred modality to evaluate for renal anomalies and hydronephrosis. It helps to differentiate hydronephrosis from tumor, multicystic dysplastic kidney and other cystic kidney diseases, while enabling assessment of abnormalities and/or compensatory hypertrophy of the contralateral kidney. 99mTc-diethylenetriaminepentaacetic acid (DTPA) is the preferred radiopharmaceutical for diuretic renography to determine differential function of and the pattern of excretion from the affected kidney. Differential function is considered normal when 40% or more, decreased if between 10% and 40% and poor if less than 10%. PUJ obstruction is confirmed if the renal scan shows significant delay in excretion and a persistent rising curve, with or without decrease in split renal function. Micturating cystourethrogram (MCU) is considered in presence of dilated ureter, bilateral hydronephrosis or following urinary infection. An intravenous urogram (IVU) is rarely required, unless suspecting duplex system, horseshoe kidney or ectopic ureter. Antegrade pyelography may be useful if vesicoureteric junction (VUJ) obstruction is suspected.

Management

Percutaneous nephrostomy (PCN) drainage is warranted in patients with infected hydronephrosis, tense hydronephrosis with differential function less than 10% and in a solitary kidney with PUJ obstruction and low function. Differential function is reassessed 2 weeks after PCN drainage in children with PUJ obstruction to look for change in renal function following drainage. This would help to identify the need for pyeloplasty versus nephrectomy.

Most patients with hydronephrosis do not require surgery. Indications for surgery in patients with PUJ obstruction include: (1) split renal function of less than 35–40% in the affected kidney along with delayed excretion and an obstructive renogram curve, (2) deterioration in split renal function from normal to less than 35–40% function or an absolute fall in differential function by greater than 10% during follow-up; (3) renal lump, recurrent infections and/or significant pain, (4) presence of horseshoe, pelvic or crossed fused kidney; and (5) anteroposterior diameter (APD) of renal pelvis greater than 25 mm on postnatal ultrasound. Anderson-Hynes pyeloplasty is the usual procedure done either by laparoscopy or by open surgery. The principles of surgery include complete excision of the abnormal segment of the upper ureter, excision of the redundant pelvis, a dependent drainage and a wide pelviureteric anastomosis. Complications include occurrence of urine leak, infection or hemorrhage and persistence of obstruction.

With timely diagnosis and needful intervention, the prognosis for PUJ obstruction is usually satisfactory provided the preoperative function is greater than 35%. Kidneys with preoperative function of less than 15% are unlikely to show improved renal function following surgery.

ECTOPIC AND HORSESHOE KIDNEY

Ectopic kidney refers to a kidney that does not normally ascend to the retroperitoneal renal fossa at the level of the second lumbar vertebra, the most common location being pelvis. The ectopic kidney fails to rotate normally, resulting in a shift of the renal axis, directing the renal pelvis anteriorly rather than medially. Kidneys that also cross the midline are referred to as crossed renal ectopy; this may occur with or without fusion to the contralateral kidney.

Renal fusion occurs when a portion of one kidney is fused to the other. The most common fusion anomaly is the horseshoe kidney, which involves abnormal migration of both kidneys along with fusion of one pole of each kidney. This differs from crossed fused renal ectopy, which usually involves abnormal movement of only one kidney across the midline with fusion to the contralateral kidney. In more than 90% cases, fusion occurs at the lower poles and two separate ureters are maintained that traverse over the isthmus or the anterior surface of the kidneys. Fusion anomalies seldom ascend normally and are typically located at L4-L5 lumbar vertebrae or in the pelvis.

Presentation and Management

Ectopic, fused or crossed fused ectopic kidneys are usually asymptomatic and diagnosed incidentally on antenatal or postnatal ultrasound. Symptoms related to urinary tract infection, obstruction and/or renal calculi. Ultrasonography is the initial investigation. About 80% cases with horseshoe kidneys may show hydronephrosis, chiefly due to associated VUR or obstruction of the collecting system. Diuretic renography is useful to rule out significant obstruction to outflow. Patients should be monitored for occurrence of hypertension, proteinuria and deranged renal function.

Most patients have an excellent prognosis without need for intervention. Patients with VUR may benefit from continuous antibiotic prophylaxis to prevent urinary tract infections. Kidneys with significant obstruction to urine outflow may require surgical intervention.

MEGAURETER

Megaureter, or ureter greater than 7 mm in diameter, may be primary (functional or anatomic abnormality of the ureterovesical junction) or secondary (secondary to bladder or urethral abnormalities, such as neurogenic bladder or posterior urethral valves). The pathogenesis of primary megaureter is uncertain, and appears to occur due to an abnormality or delay in the development of muscles in the distal ureter around 20 weeks of gestation, leading to formation of an aperistaltic segment and functional obstruction.

The diagnosis of primary megaureter is suggested by hydro-ureteronephrosis on ultrasonography. MCU and diuretic reno-graphy help to exclude VUR and/or obstruction, assess differential renal function, and exclude secondary causes of megaureter. Patients with symptoms and asymptomatic patients with obstructed megaureter require surgical intervention. Asymptomatic patients with nonrefluxing, nonobstructed megaureters or refluxing, nonobstructed megaureters are managed conservatively with monitoring for infections and serial ultrasounds.

ECTOPIC URETER

Ectopic ureter refers to presence of ureteral orifice that is caudal to the normal insertion on the bladder trigone. This occurs when the origin of the ureteral bud from the mesonephric duct is abnormally high and separation of the bud from the duct is delayed or does not occur. Almost 75–80% of ectopic ureters are associated with duplex (double) renal collecting systems and 10% cases are bilateral. In a duplex system, the cranial ureteral bud is associated with the lower renal pole, and the caudal bud with the upper pole. Renal hypoplasia or dysplasia is common. In boys, the ectopic ureter is always above the external urinary sphincter, with 50% located in the posterior urethra. In girls, the ureteric orifice is below the external sphincter in two-thirds cases.

Ectopic ureters are detected as an incidental finding on antenatal or postnatal ultrasonography. Patients may present during infancy with urinary tract infections. Due to the location of the ureteric orifice in relation to the urethral sphincter, girls, but not boys, have incontinence. Beyond the age of toilet training, boys present with urinary tract infections, flank pain, urgency, frequency or epididymorchitis, while girls may have continuous wetness. The diagnosis is made on ultrasound. Magnetic resonance urography or intravenous urography may help in resolving the diagnosis in difficult cases. Dimercaptosuccinic acid (DMSA) scintigraphy helps to detect reflux associated scarring, and locate an ectopic kidney. Diethylene triamine pentaacetic acid (DTPA) renography is useful for assessing differential function.

Treatment

Symptomatic patients often require surgery. The approach depends upon whether the collecting system is duplex or single, and the extent of renal function. Ectopic ureter in a duplex system may be associated with a dysplastic upper pole renal segment that requires excision along with the proximal ureter. If the polar segment has good function, the ectopic ureter is reimplanted into the bladder or anastomosed outside the bladder to the normal pole ureter (ureteroureterostomy). An ectopic ureter associated with a small poorly functional kidney may require nephroureterectomy. If renal function is preserved, the distal ectopic ureter is resected and reimplanted into the bladder.

BLADDER EXSTROPHY

Bladder exstrophy is characterized by a defect of the anterior abdominal wall, bladder and urethra below the umbilicus in which urine constantly dribbles on to the abdominal skin leading to local infection and ammoniacal dermatitis. The urethra is not formed completely and its meatus is on the dorsal aspect. The exstrophy epispadias complex is caused by embryological defect in abdominal wall development and persistent cloacal membrane that prevents migration of the mesenchymal tissue toward the midline. Rupture of the cloacal membrane results in herniation of lower abdominal components to the wall and characteristic features.

Boys have a short flattened penis bent toward the dorsal aspect (chordee). In the female, the clitoris is bifid, the urethral opening is located dorsally between the clitoris and labia minora (epispadias) and the anus and vagina are anteriorly displaced. The pelvic pubic rami are widely separated and the umbilicus is displaced upward. Associated problems include inguinal hernia and undescended testes, anterior looking anus and rectal prolapse. Complications include VUR, urinary tract infections, small bladder capacity, urinary incontinence, bladder stones and genital and reproductive problems. Ultrasonography helps to detect renal anomalies and hydroureteronephrosis. It also assesses bladder capacity and postvoid residue following bladder closure. DTPA and DMSA scintigraphy, MCU and urodynamic studies are required.

The goals of reconstruction are closure of the bladder and urethra, closure of abdominal wall while ensuring preservation of kidneys, urinary continence, sexual function and improved appearance of genitalia. Staged repair involves closure of bladder and abdomen at 24–48 hours of life, epispadias repair (2–3 years) and bladder neck repair (4–5 years) with or without bladder augmentation.

POSTERIOR URETHRAL VALVES

Posterior urethral valves (PUV) are obstructing membranous folds within the lumen of posterior urethra. It is the most common cause of urinary tract obstruction in newborns as well as chronic kidney disease (CKD) due to urinary tract obstruction in children. PUV appear to develop at 9–14 weeks of gestation due to an obstructing persistent urogenital membrane that disrupts the normal embryologic development of the male urethra. Proposed alternative causes include overgrowth of urethrovaginal folds and abnormal integration of the Wolffian duct into the posterior urethra.

With widespread use of antenatal ultrasonography, PUV are increasingly detected prior to birth. In developing countries, patients present in the neonatal period or infancy with poor urinary stream, abdominal distension or respiratory distress due to lung hypoplasia. Often these symptoms are ignored and presentation delayed to late childhood with features of uremia. Many cases are suspected antenatally and the diagnosis confirmed on postnatal ultrasound and MCU **(Fig. 1)**.

Management

Fetal intervention for obstructive uropathy is associated with high risk of fetal and maternal morbidity without proven benefit for long-term renal outcome. Initial postnatal management includes stabilization of the patient, drainage of the urinary tract by placement of a catheter and confirmation of the diagnosis. Management includes correction of dyselectrolytemia, particularly hyperkalemia and interventions for respiratory distress and urosepsis. Renal function is monitored before, during bladder drainage, and after valve ablation.

Direct visualization of PUV by cystoscopy confirms the diagnosis. The decision to conduct primary ablation of valves, the preferred initial surgery, depends on birthweight, patient condition and caliber of the urethra to accommodate the cystoscope. A Fogarty catheter can be used under direct visual guidance of a neonatal cystoscope to ablate the valves even in preterm babies. If, primary valve ablation is not possible particularly in premature babies, a vesicostomy is done. Higher diversion with cutaneous loop ureterostomies are indicated with poor renal function and severely dilated and tortuous upper tracts that are unlikely to drain with vesicostomy or valve ablation.
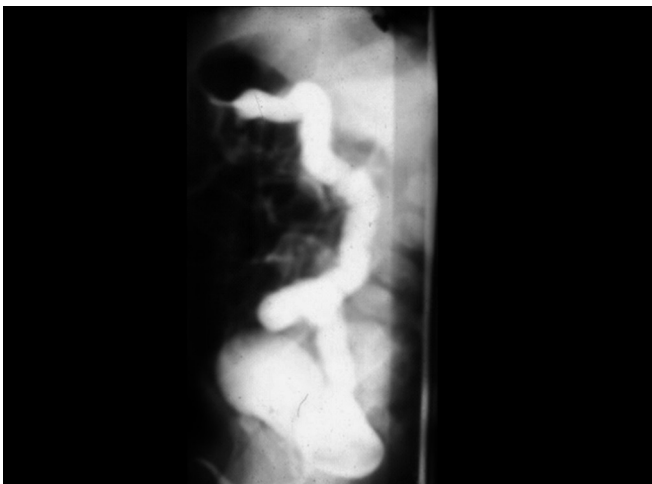
Figure 1 Micturating cystourethrogram depicting gross vesicoureteric reflux in a patient with posterior urethral valves

Complications

About 33–50% of patients with PUV have secondary VUR. Chronic kidney disease is common in patients with PUV because of *in utero* renal dysplasia and/or acquired renal scarring due to infections or poor bladder function postoperatively. About 15–20% patients progress to end-stage renal disease. Bladder outlet obstruction results in muscular hypertrophy of the bladder wall with trabeculations, diverticula and collagen deposition. These changes lead to uninhibited bladder contractions (overactive bladder) and/or non-compliance that may persist despite relief of obstruction. Urodynamic findings demonstrate low capacity, poorly compliant bladders and high filling pressure.

Prognosis

All patients with PUV are at risk for developing CKD, and an initial creatinine of greater than 1 mg/dL at presentation and its persistent elevation after relief of urinary obstruction suggest increased risk for end-stage renal disease. A significant number of patients have persistent bladder dysfunction that requires clean intermittent catheterization and anticholinergic medications.

TESTICULAR MALDESCENT

An undescended testis is one that has remained high along its line of descent and has not reached the bottom of the scrotum. The incidence is 2.7–3% at birth in full term infants and decreases to 1% at 1 year of age. Undescended testes are common in premature infants, affecting 100% infants with gestational age of less than or equal to 32 weeks. An ectopic testis is one that has deviated from its path of descent, usually to the thigh, perineum, base of penis, or even the other side of the scrotum. The most common site is the superficial inguinal pouch. An ascending testis is one that had descended normally to the scrotum at birth, but ascends progressively to be located high in inguinal canal by childhood due to lack of elongation of the spermatic cord relative to body growth. Retractile testis refers to testis that having completed the descent process is not located in its normal scrotal position secondary to a hyperactive cremasteric reflex. Failure of testicular descent occurs because of insufficient gonadotropins and/or testosterone, dysgenetic testis or an anatomic abnormality (e.g., abnormal or malplaced gubernaculum, obstruction of inguinal canal or scrotum or short vas and/or vessels). Associated complications are:

1. *Infertility:* The higher temperature of the extrascrotal testis causes testicular dysplasia with poor development of seminiferous tubules and inadequate spermatogenesis.
2. *Trauma:* Testis located in the inguinal region is more prone to direct trauma.
3. *Torsion:* This is most likely in the postpubertal period when testicular size increases.
4. *Neoplasia:* The risk of malignancy is increased 10–20-fold on affected side and 7-fold on the contralateral side. The most common malignancy is a seminoma that develops in the second or third decade of life.
5. Hernia due to patent processus vaginalis.
6. Testicular atrophy.

Management

Since histological changes may be noted before 1 year of age, the best time for orchiopexy for inpalpable testes is by the age of 9 months. If the testis is palpable, one may wait for natural descent till the child is 12–15 months old. Early surgery carries higher risk of injury to the vessels and vas deferens (2–3%). Laparoscopy has 95% sensitivity for locating a testis or proving it absent and offers a reliable diagnostic and therapeutic option. A first stage

Fowler-Stephens' procedure is performed easily and effectively using a laparoscope; the second stage is done 6 months later.

Following orchiopexy, 2% cases recur and 2–5% show testicular atrophy. Fertility is preserved in 70–80% cases with unilateral and 40% after bilateral repair. The higher the location of the gonad, the greater is the risk of malignancy and infertility. Chances of fertility are minimal if orchiopexy is delayed beyond puberty in patients with bilateral maldescent.

PREPUTIAL ADHESION

At birth, the meatus should be visible at the glans even without preputial retraction. The natural separation of prepuce from the glans continues and is completed by 2-year of age. Preputial adhesion is present if the prepuce cannot be retracted fully beyond this age or balloons out on micturition. This adhesion, affecting 1–2% boys, is distinct from phimosis that refers to excessive tightness of the foreskin preventing its retraction behind the glans.

Most adhesions are mild and are usually managed by simple separation and retraction. The presence of epithelial debris at the coronal sulcus may cause irritation and infection. Forced retraction worsens the condition by producing tears in the foreskin that heal with scarring and contraction, leading to phimosis. Simple dilatation of the foreskin using aseptic precautions is useful in cases with pooling of urine and repeated attacks of balanoposthitis. Beyond the age of 2 years, adhesinolysis (stretching and forcibly separating the glans from the inner layer of prepuce) can be done as an outpatient procedure. Daily retraction and cleansing of the glans is essential during the subsequent 10–15 days to prevent recurrence. Following retraction the prepuce must be repositioned back on to the glans to avoid paraphimosis. Circumcision is recommended in cases with recurrent urinary infection, failure of adhesinolysis, in presence of balanitis xerotica and if the prepucial skin is scarred.

Hypospadias

Hypospadias refers to an abnormal ventral location of the urethral opening. The displaced urethral meatus may be located anywhere within the glans, shaft of penis, scrotum or perineum. With an incidence of 1 in 150 to 300 livebirths, it is among the most common congenital anomalies. Urethroplasty should be performed before school-going age. Most cases have acceptable cosmetic and functional outcome following repair.

ANTENATAL HYDRONEPHROSIS

Based on the criteria used, hydronephrosis is identified in 0.6–5.4% of pregnancies. However, the majority of cases (41–88%) resolve without sequelae, representing transient physiological obstruction or stasis. Other etiologies include PUJ obstruction, 10–30%, VUR, 10–20%, VUJ obstruction or megaureter (5–10%), duplex kidneys and/or ureterocele (2–7%), and PUV (1–2%). The Indian Society of Pediatric Nephrology (ISPN) recommends classifying antenatal and postnatal hydronephrosis using classification systems based on fetal renal pelvic APD and Society of Fetal Urology (SFU) grading systems, respectively **(Table 1 and Figs 2A to D)**. Antenatal management focuses on ultrasonographic monitoring for progression of hydronephrosis, detection of other extrarenal anomalies, signs of lower urinary tract obstruction (e.g., oligohydramnios, dilated thick-walled bladder, keyhole sign, urinoma) and/or loss of renal parenchyma (e.g., cortical thinning, poor corticomedullary differentiation, increased renal echogenicity, cysts). Pregnancy in fetuses with unilateral or bilateral ANH should proceed to term, except if complicated by severe oligohydramnios or major structural anomalies. Since antenatal diagnostic and therapeutic interventions have not

Table 1 Classification of antenatal hydronephrosis, based on renal pelvic anteroposterior diameter

	Renal pelvic anteroposterior diameter (APD)	
	Second trimester	*Third trimester*
Mild	4–6 mm	7–9 mm
Moderate	7–10 mm	10–15 mm
Severe	> 10 mm	> 15 mm

been demonstrated to impact long-term outcomes, these should be considered for fetuses with suspected lower urinary tract obstruction and oligohydramnios only at specialized centers.

While all infants with antenatal hydronephrosis should have postnatal ultrasound during the first week of life, ultrasonography is performed within 24–48 hours of birth in patients with suspected posterior urethral valves, oligohydramnios or severe bilateral hydronephrosis. Ultrasonography should evaluate for SFU grade **(Figs 2A to D)**, calyceal or ureteric dilation, cortical cysts, renal echogenicity and bladder wall abnormalities. Neonates with normal ultrasound examination in the first week of life should undergo a repeat study at 4–6 weeks. Infants with isolated mild unilateral or bilateral hydronephrosis (APD < 10 mm or SFU grade 1–2) should be followed by sequential ultrasound examinations alone as spontaneous resolution occurs by 2–5 years of age in most. Neonates with unilateral or bilateral hydronephrosis with renal pelvic APD greater than 10 mm, SFU grade 3–4 or ureteric dilatation should undergo an MCU at 4–6 weeks of life to detect VUR. If reflux is ruled out, a diuretic renal dynamic scan is done at 6–8 weeks to detect significant PUJ or VUJ obstruction. The differential function is estimated and renogram curve inspected for pattern of drainage. Surgery is indicated for obstructive drainage pattern associated with low or deteriorating differential function on renography, lower urinary tract obstruction, and VUR associated with recurrent UTI despite prophylaxis. Infants with VUR or severe PUJ obstruction should receive continuous antibiotic prophylaxis. Parents of these infants should receive counseling regarding risk of urinary infections and need for prompt management. **Flow chart 1** summarizes recommendations of the ISPN for postnatal evaluation and management of antenatally diagnosed hydronephrosis.

IN A NUTSHELL

1. Congenital anomalies of kidney and urinary tract constitute 20–30% of all anomalies identified in the prenatal period. Routine antenatal ultrasonography during pregnancy detects most anomalies.
2. All patients with antenatal hydronephrosis require postnatal evaluation by ultrasonography within the first week of life. Ultrasound is recommended within 24 hour of birth for infants with bilateral involvement, a solitary affected kidney or history of oligohydramnios.
3. Infants with suspected congenital anomalies of kidney and urinary tract should undergo renal function tests at end of first week of life.
4. All patients with congenital anomalies of kidney and urinary tract should receive regular follow-up for development of hypertension, proteinuria or renal dysfunction, anthropometry and evolution of underlying abnormality.

MORE ON THIS TOPIC

Gupta DK, Sharma S. Pediatric Urology. In: Goel KG, DK Gupta, (Eds). Hutchison's Pediatrics. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2011. pp. 244-57.
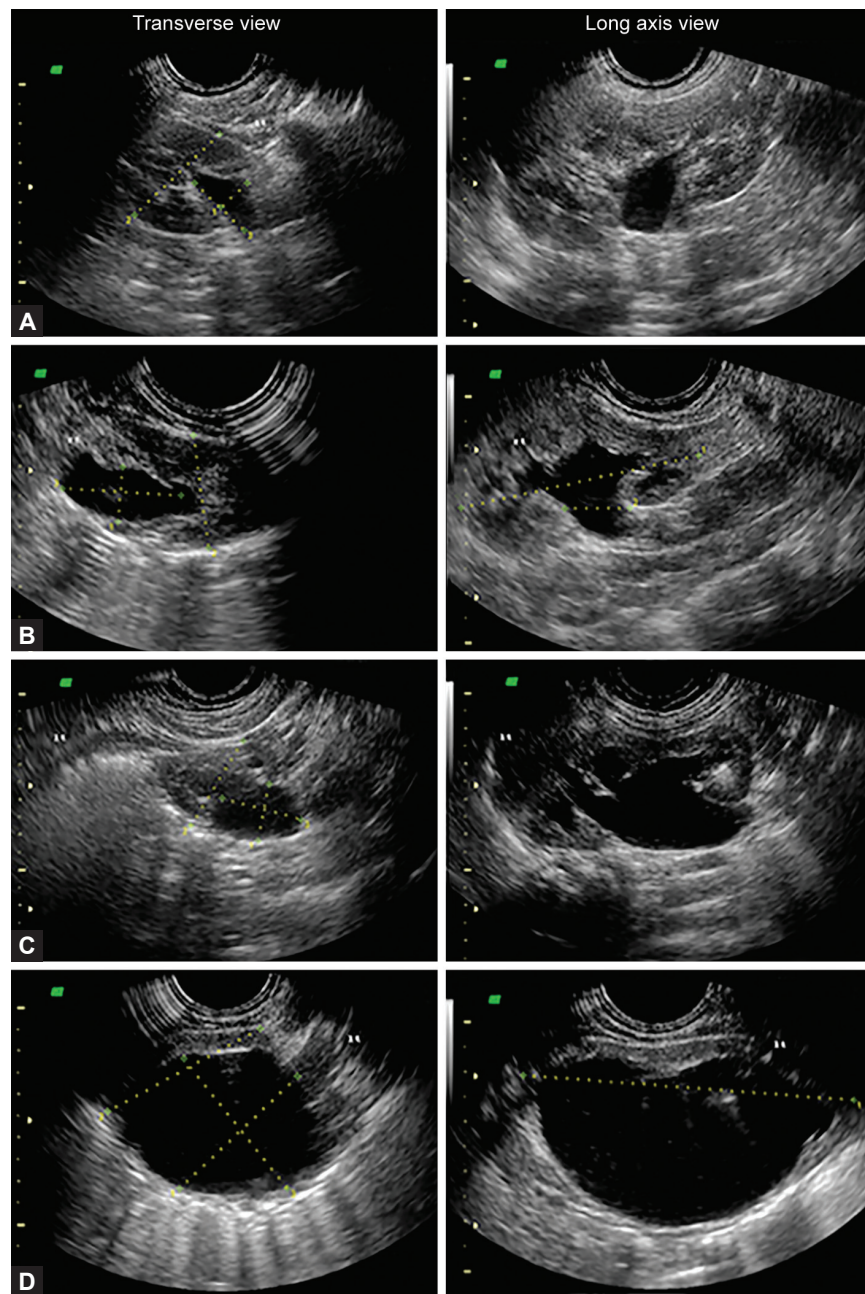
Figures 2A to D Postnatal ultrasounds depicting the different grades of hydronephrosis according to the Society of Fetal Urology classification. (A) *Grade 1:* Slight separation of the central renal echo complex; (B) *Grade 2:* Renal pelvis is further dilated and a single or a few calyces may be visualized; (C) *Grade 3:* Renal pelvis is dilated and there are fluid filled calyces throughout the kidney, but renal parenchyma is of normal thickness; (D) *Grade 4:* As grade 3, but renal parenchyma over the calyces is thinned [Reproduced with permission from Indian Pediatrics. 2013;50:215-31. Revised Guidelines on Management of Antenatal hydronephrosis]

Gupta DK, Sharma S. Fetal surgery. In: Gupta RL, (Ed). Recent Advances in Surgery. 10th ed. New Delhi; Jaypee Brothers Medical Publishers; 2006. pp.116-29

Gupta DK, Sharma S. Postoperative outcome following pyeloplasty in children using miniflank incision and transanastomotic stent: a prospective observational study. Pediatr Surg Int. 2011;27:509-12.

Gupta DK, Sharma S. Vesico-Ureteric Reflux. In: Sinha CK, Davenport M, (Ed). Handbook of Pediatric Surgery. Germany: Springer; 2010. pp. 287-91.

Gupta L, Sharma S, Gupta DK. Is there a need to do routine sonological, urodynamic study and cystourethroscopic evaluation of patients with simple hypospadias? Pediatr Surg Int. 2010;26:971-6.

Keilani R, Carachi R, Gupta DK, et al. Practical Problems In: Keilani R, Carachi R, Gupta DK, Broadis E, Sharma S, (Eds). Pediatric Surgery: An Atlas and Mindmaps. New Delhi: Jaypee Brothers Medical Publishers; 2009.

Nickavar A, Otoukesh H, Sotoudeh K. Validation of initial serum creatinine as a predictive factor for development of end stage renal disease in posterior urethral valves. Indian J Pediatr. 2008;75:695-7.

Sinha A, Bagga A, Krishna A, et al. Indian Society of Pediatric Nephrology. Revised guidelines on management of antenatal hydronephrosis. Indian Pediatr. 2013;50:215-31.

Flow chart 1 Postnatal evaluation in patients with antenatal hydronephrosis. Postnatal ultrasound is recommended at 3–7 days except if suspected lower urinary tract obstruction, when it is done earlier. Postnatal hydronephrosis is classified using Society of Fetal Urology grade or renal pelvic anteroposterior diameter (APD). Infants with normal findings should undergo a repeat study at 4–6 weeks. Patients with isolated mild hydronephrosis (unilateral or bilateral) should be followed with sequential ultrasounds, at 3- and 6-month, followed by 6–12 monthly until resolution; those with worsening hydronephrosis require closer evaluation. Patients with higher grades of hydronephrosis or dilated ureter(s) are screened for underlying obstruction or VUR. Diuretic renography is useful in detecting PUJ or VUJ obstruction and determining the need for surgery.
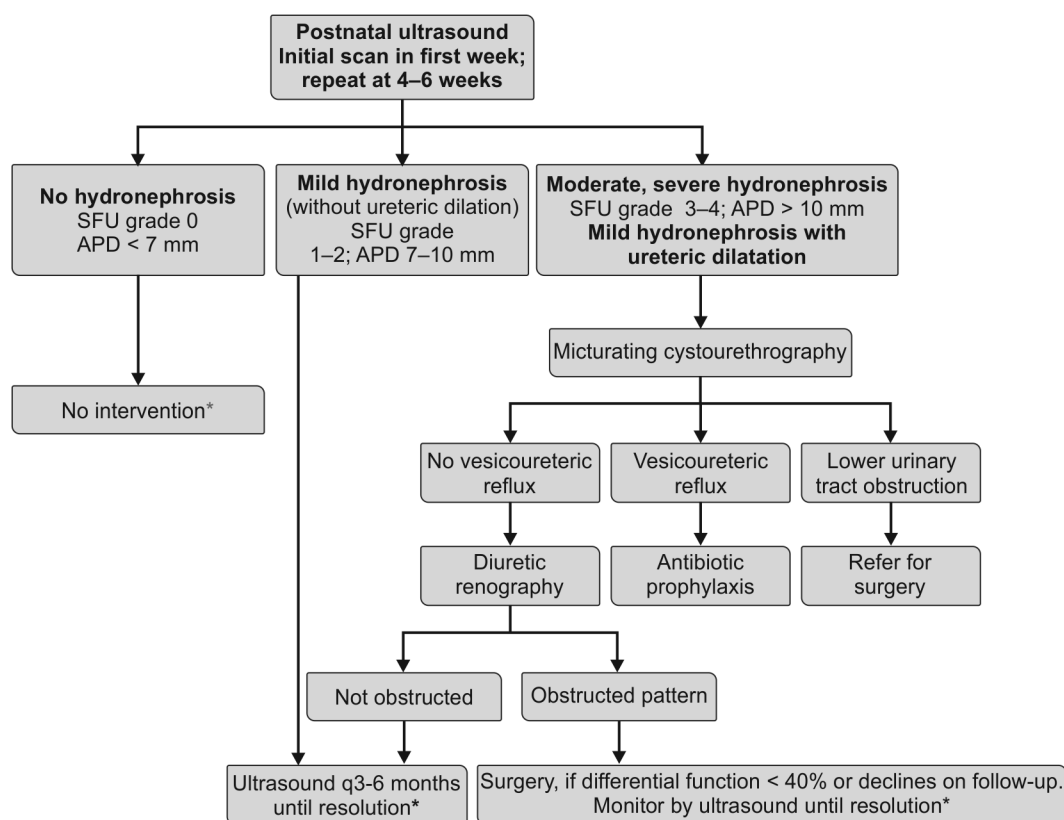
*Parents of infants with hydronephrosis should be counseled regarding the risk of urinary tract infections. [Reproduced with permission from Indian Pediatrics. 2013;50:215-31. Revised Guidelines on Management of Antenatal hydronephrosis].

Chapter 41.4
Cystic Kidney Diseases
Shina Menon

Renal cystic diseases comprise a group of sporadic and genetically determined congenital and acquired disorders characterized by the presence of cysts in one or both kidneys. For a clinician it is most beneficial to group them into genetic and nongenetic disorders **(Table 1)** as the approach to diagnosis and management is based on this.

PATHOGENESIS

Cysts, derived primarily from tubules, are epithelium-lined cavities filled with fluid or semisolid matter. Depending on the underlying disorder, cysts may develop in any part of the tubule between the Bowman's capsule and the tip of the renal papilla. There is no single mechanism for cyst formation, and it can be mediated by various inherited or acquired defects. The processes necessary for development and progression of renal cysts include proliferation of epithelial cells in segments of renal tubule, accumulation of fluid within this segment and irregularities in the organization of extracellular matrix.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder with an estimated worldwide prevalence between 1:400 and 1:1,000. It affects all races, and the annual incidence of end-stage renal disease (ESRD) secondary to ADPKD is between 6 and 8.7 per million in United States and Europe. Data from India and other south Asian countries shows that 2–5% of all ESRD is attributed to ADPKD.

Genetics

It is inherited as an autosomal dominant trait with complete penetrance. About 5–10% of patients have no family history, suggesting a high spontaneous mutation rate. It is genetically heterogeneous with two known genes; *PKD1* on chromosome 16p13.3 causes 85% cases and *PKD2* on chromosome 4q21, around

Table 1 Classification of cystic kidney diseases

Genetic
Autosomal dominant
• Autosomal dominant polycystic kidney disease (ADPKD)
• Other systemic disorders: Tuberous sclerosis, von Hippel-Lindau disease
Autosomal recessive
• Autosomal recessive polycystic kidney disease (ARPKD)
• Juvenile nephronophthisis
Associated with multiple malformation syndromes
• Chromosome disorders: Trisomy 18
• Autosomal recessive: Bardet-Biedl syndrome, Meckel-Gruber syndrome, Jeune syndrome, Joubert syndrome
• X-linked syndromes: Orofacial digital syndrome
Nongenetic
• Multicystic dysplasia
• Medullary sponge kidney
• Simple renal cysts
• Hypokalemic cystic disease
• Acquired renal cystic kidney disease (in patients with chronic kidney disease)

15%. *PKD1* causes a more rapidly progressive form of the disease with earlier cyst formation and onset of ESRD at a mean age of 54 years. The mean age of ESRD onset with *PKD2* is 74 years.

Clinical Features

Autosomal dominant polycystic kidney disease is a systemic disorder with renal and extrarenal manifestations. The intrafamilial variability in the severity of manifestations suggests both genetic and environmental modifying factors. The cysts in ADPKD are distributed throughout the cortex and medulla, and most renal manifestations are related to their enlargement. Common symptoms are chronic flank pain, hematuria, infection, nephrolithiasis and hypertension. Some symptoms, especially pain, are proportionate to the kidney size, and patients may get some relief from cyst decompression. Hematuria can be microscopic or gross, secondary to cyst hemorrhage, infection or nephrolithiasis. Early in the course of the disease, impaired urinary concentrating ability and glomerular hyperfiltration is seen.

The most common extrarenal manifestation is hepatic cysts, which are rarely seen in children, and are noted more frequently with increasing age and declining renal function. Polycystic liver disease is usually asymptomatic, but symptoms may be seen due to mass effect from the enlarged cysts, or obstructive jaundice from bile duct compression. Cyst hemorrhage, infection, and rarely torsion may occur. Occasionally, cysts may be present in other organs like pancreas, seminal vesicles and arachnoid.

Intracranial aneurysms, usually asymptomatic, may be seen in 5–15% ADPKD patients. They may sometimes cause focal findings like cranial nerve palsy or seizure from compression of local structures. Rupture of an aneurysm may lead to subarachnoid hemorrhage and present with headaches, seizures and altered sensorium.

Diagnosis

The specific diagnosis of ADPKD requires an assessment of extrarenal manifestations, age at presentation, and family history. For patients presenting at a younger age, ultrasound screening of asymptomatic parents or grandparents may be required. Specific diagnostic criteria are based on the number of cysts and age at presentation.

Genetic testing by direct sequencing detects mutations in more than 90% of affected individuals. It can be used when the imaging results are equivocal and when a definite diagnosis is required in a younger individual, such as a potential living related kidney donor. Such testing is expensive, and is not available easily in developing countries.

Treatment

There is no known cure for ADPKD, and the current therapy is directed toward mitigating the complications of ADPKD and delaying the onset of ESRD. Hypertension, which can worsen renal function, and predispose the patient to intracranial hemorrhage, should be managed aggressively. ACE inhibitors or angiotensin receptor blockers may be preferred due to their effect on increasing renal blood flow, safety profile and renoprotective properties.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral, symmetrically enlarged, poorly functioning kidneys in infants, and is associated with some degree of congenital hepatic fibrosis. It has a spectrum of severity, with the most severe forms presenting in the neonatal period. Occasionally it may present later in childhood. The incidence of ARPKD varies from 1 in 10,000 to 50,000 livebirths.

Genetics

It is transmitted as an autosomal recessive trait, and mutations in a single gene, *PKHD1* (chromosome 6p12) are responsible for the disease. *PKHD1* produces a protein called fibrocystin (or polyductin), whose disruption mediates cystogenesis through ciliary dysfunction in the renal epithelial cell.

Clinical Features

Autosomal recessive polycystic kidney disease is often noted antenatally with the affected fetus showing enlarged, echogenic kidneys with oligohydramnios. The fetus may have features of Potter sequence with characteristic facies, limb deformities and pulmonary hypoplasia. Up to half of the affected babies may not survive the neonatal period due to uremia or respiratory failure. Surviving children often have significant hypertension and chronic kidney disease (CKD), along with liver disease and portal hypertension secondary to congenital hepatic fibrosis, biliary ectasia and periportal fibrosis. A small group presents later with predominantly hepatic features or complications of portal hypertension.

Diagnosis

The diagnosis is suspected on antenatal ultrasound examination. The kidneys are enlarged with diffusely increased echogenicity, and there is associated oligohydramnios. It may sometimes appear similar to other renal cystic diseases. In such cases, the family history, evaluation of the liver for hepatic fibrosis, and absence of extrarenal malformations associated with other syndromes help to confirm the diagnosis.

Treatment

In the absence of specific therapy for ARPKD, the goals of management are early diagnosis and treatment of complications of hypertension, ESRD and portal hypertension. The prognosis of ARPKD for children who survive the first month of life has improved in recent years. Infants with massive kidneys resulting in respiratory and nutritional compromise may benefit from nephrectomy (unilateral or bilateral). For infants with ESRD, peritoneal dialysis is required until renal transplantation. Transplant outcomes in these patients are similar to those undergoing transplant secondary to other renal diseases. Older children may require surgical management of portal hypertension.

JUVENILE NEPHRONOPHTHISIS/MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX

Juvenile nephronophthisis (NPH) and medullary cystic kidney disease (MCKD) comprise a group of diseases with similarities in renal morphology but variations in the modes of inheritance, age of onset and extrarenal manifestations.

Genetics

Nephronophthisis shows an autosomal recessive inheritance, presents in childhood, and progresses to ESRD before the age of 25. Multiple genes have been identified for various forms of NPH. Medullary cystic disease is caused by mutations in either the *MCKD1* or *MCKD2* genes and has an autosomal dominant mode of inheritance.

Clinical Features

Urinary concentrating defect leading to polydipsia and polyuria, along with significant salt wasting is one of the earliest manifestations. There is progressive renal failure with growth retardation, anemia and hypertension. The urine sediment is bland. Numerous extrarenal manifestations have been reported in association with NPH. Retinitis pigmentosa is the most common and the condition is referred to as renal retinal or Senior-Loken syndrome. NPH can also be a part of other syndromes like Bardet-Biedl syndrome (with obesity, mental retardation, polydactyly, retinitis pigmentosa, hypogenitalism), Cogan syndrome (with ocular apraxia) and Joubert syndrome (with coloboma and cerebellar ataxia). These associations are not seen with medullary cystic disease.

Diagnosis

Diagnosis of NPH is usually suspected in a child or adolescent with ESRD and extrarenal manifestations as described above. Ultrasound may show nonspecific findings of normal to small sized kidneys with loss of corticomedullary differentiation, increased parenchymal echogenicity and small cysts at the corticomedullary junction. Renal biopsy is usually not performed, but it may show irregular thickening and attenuation of tubular basement membrane, chronic tubulointerstitial nephritis and tubular atrophy.

Management

Management is supportive focusing on issues related to chronic kidney disease and need for renal replacement therapy.

OTHER CYSTIC KIDNEY DISORDERS

Medullary Sponge Kidney

Medullary sponge kidney (MSK) is characterized by nonprogressive dilatation of tubules and distal collecting ducts, associated with cysts and diverticula in the medullary pyramids. It usually occurs as a sporadic disorder, though it may be associated with other congenital anomalies, such as Beckwith-Wiedemann syndrome, Ehlers-Danlos syndrome, anodontia and Caroli disease. It is often asymptomatic, and may remain undetected. Some patients may present with renal colic, hematuria, urinary tract infections and nephrolithiasis. Up to 50% of the patients have hypercalciuria, which along with urinary stagnation in the dilated tubules and incomplete distal renal tubular acidosis may predispose to stone formation.

The diagnosis of MSK is confirmed on intravenous pyelography, which shows enlarged kidneys, characteristic brush-like linear striations, papillary contrast blush and persistent medullary opacification. Management of MSK involves management of nephrolithiasis and urinary infections. When managed and followed up appropriately, MSK does not lead to renal insufficiency.

Multicystic Dysplastic Kidney

Multicystic dysplastic kidney (MCDK) is a developmental anomaly resulting in multiple cysts of varying sizes, without identifiable normal renal parenchyma. It is believed to be a result of severe obstructive hydronephrosis secondary to atresia of the ureter or renal pelvis. It is proposed that MCDK results from abnormal interaction between the ureteric bud and metanephric mesenchyme. The affected kidney is nonfunctional, with the contralateral kidney working normally and showing compensatory hypertrophy. It is one of the most common causes of an abdominal mass in a newborn.

Multicystic dysplastic kidney is often diagnosed on prenatal ultrasonography or may sometimes be diagnosed incidentally on an ultrasound done for unrelated reasons. The contralateral system is abnormal in one-third patients with anomalies like ureteropelvic junction obstruction and vesicoureteral reflux. Voiding cysto-

urethrogram and a radioisotope scan are recommended as part of the work-up, particularly if the contralateral kidney is abnormal on the ultrasound.

Multicystic dysplastic kidney has a benign course and the incidence of complications is extremely rare. Almost half undergo spontaneous involution. While there are anecdotal case reports, large series data indicate that MCDK is not associated with an increased risk for hypertension or neoplasm.

Simple Cysts

Simple cysts are rare in children and are usually detected as an incidental finding on an ultrasound. They may be single or multiple, but their characteristic feature is the presence of smooth walls with no internal echoes. Rarely, they may cause hematuria or flank pain.

Acquired Cystic Kidney Disease

Acquired cystic kidney disease is characterized by presence of multiple small cysts in the renal cortex and medulla of patients with ESRD, unrelated to inherited renal cystic diseases. Acquired cysts are found in 10–20% of patients with CKD, and the prevalence increases with the duration of dialysis. Acquired renal cysts are also seen with chronic hypokalemia.

It is important to have a systematic approach to patients with cystic disease. A detailed family history (including ultrasonography of family members occasionally), presence of consanguinity and a pedigree chart help to determine if there is a familial basis and what the mode of inheritance is likely to be. Clues to diagnosis may be obtained from the patient age, renal function and presence of extrarenal manifestations. Further investigations are planned based on initial assessment.

IN A NUTSHELL

1. It is important to have a systematic approach to patients with cystic disease. Family history (including a pedigree chart) and presence of extrarenal manifestations provide important clues toward diagnosis.
2. Not all genetic disorders have their onset at birth, and not all congenital disorders are heritable.
3. Autosomal dominant polycystic kidney disease usually presents after the age of 30 years, but may present earlier also. It presents with hematuria, flank pain, and hypertension.
4. Autosomal recessive polycystic kidney disease presents in utero or in early infancy, though milder cases can present later in childhood. The kidneys are usually large and uniformly hyperechoic. Discrete cysts may not be visible.

MORE ON THIS TOPIC

Bergmann C, Zerres K. Polycystic Kidney Disease: ADPKD and ARPKD. In: Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. 1st ed. Philadelphia: Mosby; 2008. pp. 155-78.

Guay-Woodford L. Autosomal Recessive Polycystic Kidney Disease. In: Flinter F, Saggar-Malik A. The genetics of renal disease. Oxford (UK): Oxford University Press; 2003. pp. 239-51.

Hildebrandt F. Nephronophthisis and Medullary Cystic Kidney Disease. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N. Pediatric Nephrology. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2009. pp. 831-48.

Rosenblum ND, Salomon R. Disorders of Kidney Formation. In: Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. 1st ed. Philadelphia: Mosby; 2008. pp. 131-42.

Torres VE, Grantham JJ. Cystic Diseases of the Kidney. In: Brenner BM. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008. pp. 1428-62.

Chapter 41.5
Hematuria
Rajiv Sinha

Hematuria can be either gross (macroscopic) when it can be appreciated by naked eye or microscopic when red blood cells (RBC) are detected only on urine microscopy. The color of urine helps to determine the site of disease, with cola or tea color seen usually with glomerular disease, and pink or frank red color suggesting a nonglomerular cause. Microscopic hematuria is the presence of more than 5 RBC per high power field (HPF) in a centrifuged sample. Persistent hematuria is defined as the presence of microscopic hematuria in more than two samples collected over the next 2–3 weeks.

EPIDEMIOLOGY

Macroscopic hematuria has an estimated incidence of 1.3 per 1,000 children. The incidence of microscopic hematuria varies with definition. Screening programs in school children have reported persistent microscopic hematuria in 1–2% of children. The prevalence fall when the number of samples and follow-up duration are increased; 0.41% when four samples were collected and 0.14–0.32% when five specimens were analyzed.

DETECTION OF HEMATURIA

Although red urine suggests gross hematuria, it needs to be confirmed on urinalysis to differentiate from other causes **(Table 1)**. Microscopic hematuria is detected only by urinalysis including urine dipstick and microscopy. Urinary dipsticks for hemoglobin are based on oxidation of *ortho*-toluidine by organic peroxide in presence of hemoglobin that serves as a catalyst. The product of the reaction has a blue color, the intensity of which is matched against a color chart. The test can detect as little as 150 μg/L of free hemoglobin, with 100% sensitivity and 99% specificity in detecting 1–5 RBC per HPF. Since myoglobin/hemoglobin can also catalyze this oxidation process, the absence of RBC on urine microscopy in a patient with positive urine dipstick suggests myoglobinuria or hemoglobinuria. Reducing agents such as vitamin C can give false negative results. False positive results can occur if the urine sample is concentrated or following contamination with oxidizing agents such as povidone iodine or hypochlorite. RBCs are identified by their biconcave disc appearance. False negative results can occur if the urine is diluted or if urine pH is alkaline, leading to RBC lysis.

ETIOLOGY

History, examination and urinalysis help to distinguish between glomerular and nonglomerular causes of hematuria **(Table 2)**.

Table 2 Etiology of hematuria

Glomerular	Nonglomerular
Glomerulonephritis (GN)	Urinary tract infection
Postinfectious GN	Hypercalciuria
Membranoproliferative GN*	Renal calculi*
Membranous nephropathy	Hydronephrosis (rare)
IgA nephropathy*	Trauma; exercise
Systemic lupus erythematosus	Renal vein thrombosis
Henoch-Schönlein purpura	Chemical cystitis, e.g., cyclophosphamide
Wegener granulomatosis; renal vasculitis	Interstitial nephritis
Hemolytic uremic syndrome	Coagulopathy
Alport syndrome*	Vascular malformations*
Cystic renal disease*	Nutcracker syndrome*
Familial hematuria (thin basement membrane disease)*	Tuberculosis* Wilms tumor; rhabdomyosarcoma
Nonfamilial benign hematuria	False: Menstruation; factitious

* Recurrent hematuria

Glomerular hematuria is likely if RBC casts are present and/or more than 20–30% of RBCs are dysmorphic (more easily identified under phase contrast microscope). Systemic manifestations like fever, pharyngitis, edema, rash and arthritis are more commonly associated with glomerular disease. The most common causes of gross hematuria are renal calculi and IgA nephropathy; however, postinfectious glomerulonephritis remains an important etiology among children from developing regions. Thin basement membrane nephropathy is the most common cause of persistent asymptomatic microscopic hematuria.

EVALUATION OF A CHILD WITH HEMATURIA

The emphasis of evaluation is on identifying common and treatable causes while avoiding unnecessary expensive and invasive interventions where the etiology is more likely to be benign. Significant family history, findings like colic, painful micturition, rash or joint pains, and the presence of hypertension, significant proteinuria and/or azotemia are considered as *red flag signs* and these patients are evaluated in greater detail. Children with hematuria can present in the following ways: (i) gross hematuria (red or dark-colored urine); (ii) microscopic hematuria in a symptomatic child; and (iii) an asymptomatic child with incidental finding of microscopic hematuria. A stepwise approach **(Flow chart 1)** helps to identify important etiologies while avoiding unnecessary evaluation.

Gross Hematuria

The first step is to confirm the presence of *true* hematuria on urine microscopy. Urinalysis also helps to distinguish between

Table 1 Causes of urinary discoloration

Color	Pathologic causes	Foods and drugs
Cloudy	Phosphaturia, pyuria, chyluria, lipiduria, hyperoxaluria	Diet high in purine-rich foods (hyperuricosuria)
Brown	Bile pigments, myoglobin	Fava beans; levodopa, metronidazole, nitrofurantoin
Brownish black	Bile pigments, melanin, methemoglobin, alkaptonuria, homogentisic acid	Levodopa, methyldopa, senna
Green, blue	Urinary infection with *Pseudomonas*, biliverdin	Amitriptyline, IV cimetidine, promethazine, indigo, methylene blue, triamterene
Red	Hematuria, hemoglobinuria, myoglobinuria, porphyria	Beets, blackberries, rhubarb; phenolphthalein, rifampicin
Dark yellow, orange	Concentrated urine	Carrots, rifampicin

Flow chart 1 Workup for a patient with red colored urine
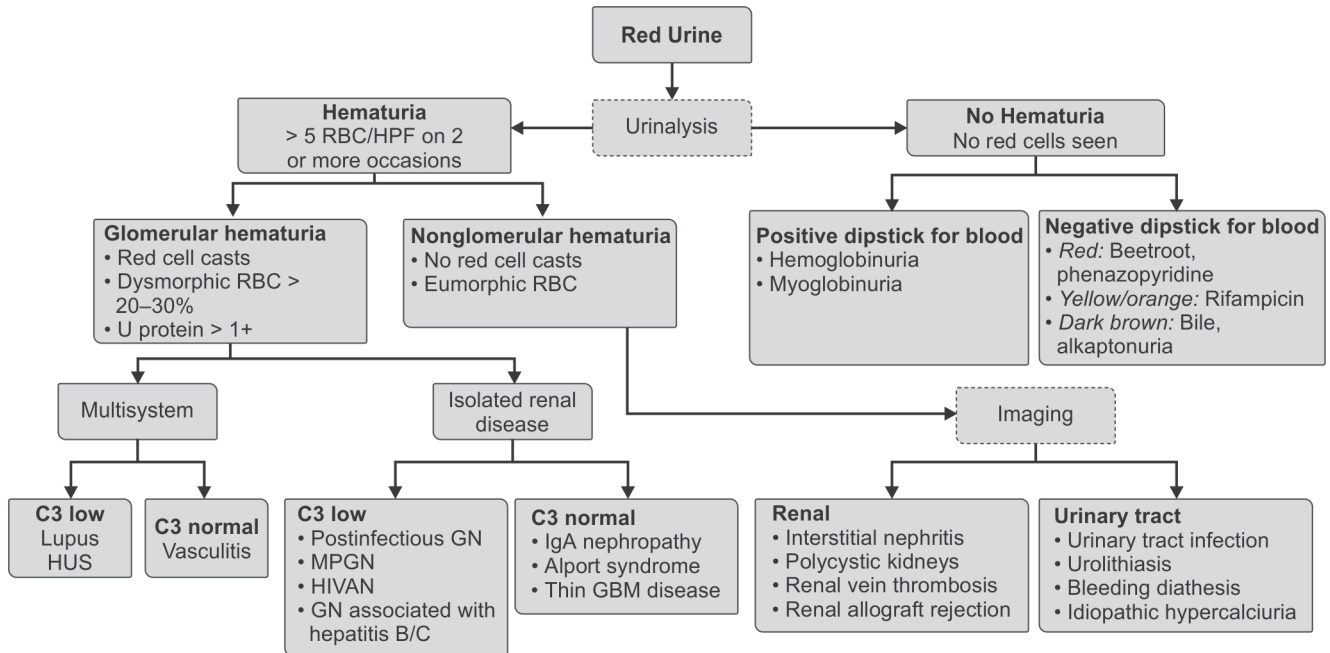
Abbreviations: MPGN, membranoproliferative glomerulonephritis; HIVAN, HIV-associated nephropathy; GBM, glomerular basement membrane; HUS, hemolytic uremic syndrome.

glomerular or nonglomerular etiology **(Flow chart 1)**. Although gross hematuria may be associated with up to 2+ proteinuria, 3–4+ proteinuria signifies glomerular origin. The presence of edema or hypertension with or without azotemia suggests glomerulonephritis and the investigations should be directed toward identifying the etiology **(Flow chart 1)**. Low levels of complement C3 are commonly associated with postinfectious glomerulonephritis, but are also associated with lupus nephritis, membranoproliferative glomerulonephritis and atypical hemolytic-uremic syndrome. The presence of low levels of C4 as well as C3 suggests lupus, confirmed by testing for antinuclear antibodies. Levels of C3 return to baseline within 8–12 weeks of postinfectious glomerulonephritis; failure of C3 to normalize by 12 weeks suggests an alternate etiology and need for renal biopsy **(Box 1)**. Progressive rise in serum creatinine along with other features of glomerulonephritis suggests rapidly proliferative glomerulonephritis. Renal biopsy is essential to ascertain the diagnosis and plan specific management. Wegener granulomatosis (granulomatous polyangiitis) and other forms of pauci-immune crescentic glomerulonephritis should be considered in presence of normal complement C3 and presentation as rapidly progressive glomerulonephritis; testing for antinuclear cytoplasmic antibody (ANCA) helps confirm the diagnosis.

Dysuria, flank pain and colic are usually associated with nonglomerular etiologies such as urinary tract infection and nephrolithiasis. Other than bacterial infections, certain viruses, e.g., adenoviruses, may cause cystitis associated with gross hematuria. Patients with hypercalciuria may present with gross hematuria. The diagnosis of sickle cell hemoglobinopathy and schistosomiasis should be considered in susceptible populations. Wilms tumor may present with painless gross hematuria, while patients with rhabdomyosarcoma of the bladder often have painful voiding or other symptoms along with macroscopic hematuria. The diagnosis of these conditions is aided by a careful abdominal ultrasound. Patients with history of abdominal trauma may require CT in order to find a renal or urological lesion.

Nutcracker syndrome should be considered in children with recurrent isolated gross hematuria without an obvious cause. Compression of the left renal vein between the aorta and superior mesenteric artery resulting in left renal vein entrapment and hypertension is postulated to cause the intermittent gross or microscopic hematuria. The diagnosis is suggested by Doppler ultrasonography and/or MR angiography. Exercise induced hematuria refers to transient hematuria occurring immediately after severe exercise and is thought to be caused by RBC excretion secondary to a hyperdynamic circulation induced by the exercise. Cystoscopy should be considered in cases with persistent gross hematuria of suspected nonglomerular etiology, where routine investigations fail to provide a diagnosis.

Microscopic Hematuria with or without Symptoms

Approach to a child with microscopic hematuria and other symptoms are similar to that suggested for patients with gross hematuria. However, asymptomatic microscopic hematuria and/

BOX 1 Indications for renal biopsy in hematuria

- Significant proteinuria (except with postinfectious glomerulonephritis)
- Persistently (> 12 weeks) low serum complement C3
- Signs of systemic disease, e.g., systemic lupus erythematosus, Henoch-Schönlein purpura, ANCA (antineutrophil cytoplasmic antibody) positive vasculitis
- Family history suggestive of Alport syndrome
- Recurrent gross hematuria of unknown etiology
- Persistent microscopic glomerular hematuria and parental anxiety about diagnosis and prognosis*.

*Renal biopsy is usually not done in cases with isolated microscopic hematuria (i.e., without proteinuria or systemic manifestations).

or mild proteinuria are known to occur transiently during febrile illness or after rigorous exercise. Hence, unnecessary investigations may be avoided in patients with asymptomatic microscopic hematuria without proteinuria, emphasizing on careful follow-up on the long-term.

MORE ON THIS TOPIC

Diven SC, Travis LB. A practical primary care approach to hematuria in children. Pediatr Nephrol. 2000;14(1):65-72.

Kashtan CE. Familial hematuria. Pediatr Nephrol. 2009;24(10):1951-8.

Meyers KE. Evaluation of hematuria in children. Urol Clin North Am. 2004;31(3):559-73.

Phadke KD, Vijayakumar M, Sharma J, Iyengar A; Indian Pediatric Nephrology Group. Consensus statement on evaluation of hematuria. Indian Pediatr. 2006;43(11):965-73.

Quigley R. Evaluation of hematuria and proteinuria: how should a pediatrician proceed? Curr Opin Pediatr. 2008;20(2):140-4.

IN A NUTSHELL

1. A stepwise approach to evaluation of hematuria prevents unnecessary investigations, while decreasing the chance of missing important etiologies.
2. It is important to differentiate between glomerular and non-glomerular hematuria.
3. Ultrasound helps to rule out structural pathologies, such as obstruction, tumor and calculi.
4. Symptomatic patients with features of glomerulonephritis require detailed evaluation, including biopsy.
5. Patients with family history of hematuria require evaluation to exclude Alport syndrome and thin basement membrane disease.
6. Children with asymptomatic isolated microscopic hematuria without proteinuria are followed in a wait and watch manner without intensive investigations.

Chapter 41.6
Glomerulonephritis

ACUTE NEPHRITIC SYNDROME

Amarjeet Mehta

Nephritic syndrome is a clinical syndrome characterized by hematuria, proteinuria, edema, hypertension and impaired renal function. The underlying mechanism is glomerular injury with inflammation. In developing countries, postinfectious glomerulonephritis (GN), with an incidence of 2/100,000 person-years, accounts for 50–90% cases of nephritic syndrome in children; the incidence is much lower at 0.3/100,000 person-years in developed regions. Other etiologies of nephritic syndrome are listed in **Box 1**.

PATHOGENESIS

The hallmark of acute GN is generalized glomerular inflammation with proliferation of resident glomerular cells and infiltration by lymphocytes or neutrophils. Glomerular inflammation results from antigen-antibody reactions, which begin with antibodies binding directly or to an antigen trapped or expressed in the glomerulus, leading to activation of one or more systems of inflammatory mediators, e.g., the complement cascade, coagulation factors, cytokines or growth factors that cause glomerular injury. In most conditions, humoral as well as cellular immune responses are involved.

The pathologic correlate of acute nephritic syndrome is proliferative GN. Proliferation is initiated by neutrophils and monocytes but is caused chiefly by an increase in resident glomerular endothelial and mesangial cells. This inflammation is termed diffuse proliferative GN when it involves most of the glomeruli; less extensive involvement is termed focal prolifera-tive GN **(Fig. 1A)**. Renal biopsy shows diffuse endocapillary proliferative GN with numerous polymorphonuclear cells and

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BOX 1 Causes of acute nephritic syndrome

- Postinfectious glomerulonephritis: Poststreptococcal, infective endocarditis, shunt nephritis
- IgA nephropathy
- Henoch-Schönlein nephritis
- Systemic lupus erythematosus
- *Membranoproliferative glomerulonephritis:* Immune complex, C3 glomerulopathy
- **Small vessel vasculitides:* Microscopic polyangiitis, granulomatosis with polyangiitis
- **Crescentic glomerulonephritis:* Immune complex, pauci-immune, antiglomerular basement membrane disease
- Cryoglobulinemia.

*Typically present as rapidly progressive glomerulonephritis.

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presence of humps on external (subepithelial) side of glomerular basement membrane **(Fig. 1B)**. Immunofluorescence examination shows granular deposits of complement C3, immunoglobulin (Ig) G, and rarely, IgM and IgA. Positivity for IgG, IgA, IgM, C3, C4 and C1q, termed *full house* staining, suggests lupus nephritis. The inflammation and expansion leads to enlargement of glomeruli resulting in impaired circulation, reduced glomerular filtration rate (GFR) and retention of salt and water, fluid overload and hypertension with or without encephalopathy and pulmonary edema.

CLINICAL FEATURES

Acute postinfectious GN usually follows an upper respiratory or skin infection with a nephritogenic strain of group A β-hemolytic *Streptococcus*, with latency of 1–2 weeks and 2–6 weeks, respectively. Recent history of sore throat or skin infection, increased antistreptolysin O (ASO) and/or anti-DNAse antibody titer and marked but transient reduction in C3 and C4 levels suggest acute poststreptococcal GN. A similar presentation may be noted in membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, Henoch-Schönlein purpura and systemic lupus erythematosus (SLE). These entities are differentiated by clinical, laboratory and histological features.

Patients present with hematuria, facial edema and oliguria. The urine is described as dark, cola or tea colored, smoky or dirty. Headache, malaise and anorexia may be associated. The course of illness in patients with the acute nephritic syndrome might be complicated by severe hypertension, cardiac failure and pulmonary edema. Posterior reversible encephalopathy syndrome manifests with visual alterations, mental disturbances, severe headache and seizures; characteristic changes are seen on MRI. Patients with the acute nephritic syndrome should be distinguished from rapidly progressive glomerulonephritis (RPGN), characterized by features of the nephritic syndrome followed by rapid decline of renal function over days to weeks. These patients need prompt evaluation and therapy.

EVALUATION

Careful urinalysis is the most important investigation **(Box 2)**. The presence of red blood cells and red cell casts is characteristic. The detection of few leukocytes is not uncommon and indicates glomerular inflammation. Mild proteinuria is almost always present; nephrotic range proteinuria is uncommon. Mild anemia is frequently noted and is dilutional. Renal functions are mildly deranged or normal. Mild hypoalbuminemia may be present, but serum albumin values below 2.5 g/dL are unusual. Low levels of C3 are seen in patients with postinfectious GN, MPGN and lupus nephritis. Transient decrease in C4 levels is seen in lupus and in some patients with MPGN.

Kidney biopsy is recommended in patients with extrarenal symptoms, renal failure lasting more than 7–10 days, persistent nephrotic range proteinuria, low C3 that persists for more than 12 weeks and hematuria that does not resolve in 6 months.

BOX 2 Evaluation of acute nephritic syndrome

Initial evaluation
- Blood counts, urea, creatinine, electrolytes, albumin
- Urinalysis: Microscopy; spot urine protein: creatinine ratio; 24 hours urinary protein
- Throat culture or culture of skin lesions
- Antistreptococcal antibody titer: Antistreptolysin O, anti-DNAse B, antihyaluronidase
- Complement C3, C4

Subsequent evaluation
- Antinuclear antibody (ANA); other autoantibodies if ANA is positive
- Antineutrophil cytoplasmic antibody
- Anti-GBM antibody titer (if pulmonary involvement)
- Renal biopsy (if atypical features).

Abbreviation: anti-GBM, antiglomerular basement membrane.

TREATMENT

Most patients have subclinical disease or mild symptoms that can be managed at home or on outpatient basis. Patients with acute and severe manifestations should be hospitalized. Bed rest and restriction of fluid and sodium intake are advised. Loop diuretics [furosemide 2 mg/kg intravenously (IV) or oral, divided in two doses] are used in presence of significant edema, hypertension and/or pulmonary edema. Thiazide diuretics are usually ineffective. Prompt medical management is required for hyperkalemia, pulmonary edema and congestive heart failure.

Patients with severe hypertension require antihypertensive treatment. Nifedipine (0.5 mg/kg q6h) or hydralazine (0.1 mg/kg IV) is effective but may cause tachycardia. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are avoided due to risks of reduction in GFR and hyperkalemia. Sodium nitroprusside is effective in severe hypertension with encephalopathy. Renal replacement therapy, as hemodialysis or peritoneal dialysis, is indicated in patients with hyperkalemia, acid base imbalance, fluid overload and uremia not responding to drug therapy alone. While therapy with immunosuppressive agents is not required in patients with postinfectious GN, corticosteroids and/or other agents have been used in patients with IgA nephropathy, vasculitis and lupus nephritis. Patients with persistent proteinuria benefit from treatment with ACE inhibitors.

IN A NUTSHELL

1. Nephritic syndrome is a clinical syndrome of hematuria, proteinuria, edema, often with hypertension and a mild degree of acute kidney injury.
2. The pathologic correlate of acute nephritic syndrome is proliferative GN and its chief cause is acute postinfectious GN.
3. Hypertensive encephalopathy, hyperkalemia, pulmonary edema and uremia are uncommon but life-threatening complications.
4. Management is supportive, comprising loop diuretics, anti-hypertensive agents, fluid and salt restriction, and dialysis as required. The role of immunosuppression is limited.

MORE ON THIS TOPIC

Eison TM, Ault BH, Jones DP, et al. Poststreptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol. 2011;26:165-80.

Niaudet P. Nephritic syndrome. In: Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008. pp. 195-203.

Rodriguez-Iturbe B, Mezzano S. Acute postinfectious glomerulonephritis. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N. Pediatric Nephrology. 6th ed. Wisconsin: Springer; 2009. pp. 743-55.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Arvind Bagga, Shina Menon

Rapidly progressive glomerulonephritis is characterized by acute GN with rapid loss of renal function (more than 50% decrease in GFR over days to weeks). Histology shows the presence of crescents (crescentic GN) involving 50% or more glomeruli. This may be seen in a variety of conditions including poststreptococcal GN, renal vasculitis, IgA nephropathy, SLE and MPGN **(Box 3)**.

EPIDEMIOLOGY

The exact incidence of RPGN in children is not known. Crescentic GN comprises about 5% of unselected renal biopsies in children. Immune complex GN is the most common pattern of crescentic GN in children accounting for 75–80% of cases in most reports. Pauci-immune crescentic GN, while common in adults, is less frequent in children, accounting for 15–20% cases. Recent studies show decline in proportion of patients with immune complex GN and increasing number with pauci-immune crescentic GN.

ETIOLOGY

Based on pathology and immunofluorescence staining patterns, crescentic GN is classified into the following categories.
- *Immune-complex GN* It is a heterogeneous group characterized by proliferative GN with crescents secondary to multiple stimuli, and granular deposits of Ig and complement along capillary walls and in the mesangium on immunofluorescence. The causes include infections, systemic diseases and pre-existing primary GN **(Box 3)**.
- *Pauci-immune GN* It includes renal-limited vasculitis, and the renal manifestations of microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's granulo-

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BOX 3 Causes of rapidly progressive glomerulonephritis (RPGN)

Immune Complex GN

Postinfectious GN: Poststreptococcal nephritis, infective endocarditis, shunt nephritis, other bacterial infections, human immunodeficiency virus, hepatitis B and C, syphilis

Systemic disease: Systemic lupus erythematosus, Henoch-Schönlein purpura, mixed connective tissue disorder, juvenile idiopathic arthritis

Primary GN: IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy

Pauci-immune Crescentic GN

Microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's granulomatosis), renal limited vasculitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)

Idiopathic crescentic GN

Medications: Penicillamine, hydralazine, hydrocarbons, propylthiouracil

Antiglomerular Basement Membrane (GBM) GN

Anti-GBM nephritis, Goodpasture syndrome, postrenal transplantation in Alport syndrome

RPGN without Crescents

Hemolytic uremic syndrome

Acute interstitial nephritis

Diffuse proliferative GN.

Abbreviation: GN, glomerulonephritis.

matosis), or eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). They show few or no immune deposits on immunofluorescence. Majority of the patients have antineutrophil cytoplasmic autoantibodies (ANCA) in blood, and are collectively classified as ANCA-associated vasculitides. Approximately 10–30% of patients with pauci-immune crescentic GN are ANCA negative. These patients have fewer constitutional and extrarenal symptoms than those who are ANCA-positive.

- *Antiglomerular basement membrane (GBM) GN:* It is uncommon in childhood. It is caused by an autoantibody directed against the α3 chain of type IV collagen. Pulmonary involvement (Goodpasture syndrome) is rare. Approximately, 5% patients with Alport syndrome who have undergone a renal transplant may develop anti-GBM GN in the first year of transplant.

CLINICAL FEATURES

The typical presentation is with a nephritic syndrome that fails to resolve and presents with persistent macroscopic or microscopic hematuria, oliguria, hypertension and edema. Fluid overload and renal dysfunction may lead to hypertensive emergencies, pulmonary edema and cardiac failure. Patients with pauci-immune RPGN may have systemic symptoms at onset involving the respiratory tract (cough, sinusitis), skin (vasculitic rash), musculoskeletal (joint pain, swelling), and nervous system (seizures, altered sensorium). Those with anti-GBM GN present with hemoptysis and occasionally pulmonary hemorrhage.

INVESTIGATIONS

Rapidly progressive glomerulonephritis is a medical emergency, and a delay in instituting treatment can lead to irreversible loss of renal function. It is important to follow a rational approach towards diagnosis and management especially in resource-limited settings. The diagnosis of the etiology depends on integrating clinical data with serology and renal histology. Urinalysis shows microscopic hematuria, characterized by dysmorphic red cells and red cell casts in all patients, along with a variable degree of proteinuria (2+ to 4+), and leukocyte, granular and tubular epithelial cell casts. Renal insufficiency is usually present at diagnosis.

Serological investigations are important in evaluating the etiology and for monitoring disease activity. Total hemolytic complement and C3 are reduced in postinfectious GN, SLE and MPGN. Patients with SLE and type 1 MPGN also have low C1 and C4 due to activation of the classic complement pathway. Antinuclear antibody (ANA) and antidouble stranded DNA autoantibodies are seen in patients with SLE. ANCA is elevated in most patients with pauci-immune crescentic GN. It should be screened by indirect immunofluorescence for the staining pattern and by enzyme-linked immunosorbent assay (ELISA) for proteinase-3 (PR3) and myeloperoxidase (MPO). Granulomatosis with polyangiitis is associated with PR3 ANCA, which produces a cytoplasmic pattern (c-ANCA). MPO ANCA, with perinuclear staining (p-ANCA), is seen in renal limited vasculitis and drug-induced crescentic GN. Patients with microscopic polyangiitis have equal distribution of both types of ANCA. 10% of patients with granulomatosis with polyangiitis or microscopic polyangiitis have negative assays for ANCA. Anti-GBM IgG antibodies are seen in anti-GBM nephritis or Goodpasture syndrome and correlate with disease activity.

HISTOPATHOLOGY

Crescents may be completely cellular or may show variable scarring and fibrosis. Cellular crescents are characterized by proliferation of macrophages, epithelial cells and neutrophils, and in fibrous crescents, the cells are replaced by collagen **(Fig. 1C)**. Fibrocellular crescents show a mixture of both features. Interstitial changes range from acute inflammatory infiltrate to chronic interstitial scarring and tubular atrophy. The presence, location and nature of immune deposits on immunohistology and electron microscopy help diagnose the etiology of RPGN. *Full house* deposits of granular IgG, IgA, IgM, C3, C4 and C1q are seen in SLE; other immune complex GNs have similar characteristic deposits. Patients with vasculitis, both with and without ANCA positivity, have few or no immune deposits. Anti-GBM disease is characterized by linear deposits of IgG and C3.

MANAGEMENT

There are two components of treatment of RPGN: (1) *induction* of remission and (2) *maintenance* **(Box 4)**. Standard induction therapy includes high-dose steroids and cyclophosphamide, with additional therapy for those with life or organ-threatening disease. Both IV and oral cyclophosphamide have been used. IV therapy is more likely to induce remission and has a lower risk of infection and leukopenia. Evidence for use of other agents like rituximab, mycophenolate mofetil (MMF) and IV Ig is limited. Plasmapheresis or plasma exchange may be beneficial for patients with RPGN due to lupus, Henoch-Schönlein purpura and severe proliferative GN, and in life-threatening pulmonary hemorrhage.

The duration of maintenance therapy in crescentic GN depends on the underlying disease. Most patients with ANCA-associated disease need long-term maintenance immunosuppression due to the risk of relapses. Azathioprine is preferred over extended treatment with cyclophosphamide due to significant risks associated with the latter. MMF may also be used as an alternative for maintenance therapy in patients who have ANCA vasculitis, and who are allergic to or intolerant of azathioprine.

OUTCOME

Patients with poststreptococcal crescentic GN have a satisfactory prognosis, with most showing spontaneous improvement. Patients with pauci-immune crescentic GN, MPGN and idiopathic RPGN have less favorable outcomes than Henoch-Schönlein purpura or systemic lupus. End-stage renal disease (ESRD) may occur in the long-term in up to 25% patients with ANCA-associated vasculitis. The outcome is determined by the severity of renal

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BOX 4   Treatment of crescentic glomerulonephritis

Induction

Methylprednisolone 15–20 mg/kg (maximum 1g) IV daily for 3–6 doses

Prednisolone 1.5–2 mg/kg/day PO for 4 weeks; taper to 0.5 mg/kg daily by 3 months followed by 0.5–1 mg/kg on alternate day

*Cyclophosphamide 500–750 mg/m^2 IV every 3–4 weeks for 6 pulses

#Plasma exchange

Maintenance

Azathioprine 1.5–2 mg/kg/day for 12–18 months

Alternate day low-dose prednisolone

Consider mycophenolate mofetil (1,000–1,200 mg/m^2/day) or cyclosporine if disease activity is not controlled with azathioprine or if does not tolerate azathioprine

Agents for refractory disease

Intravenous immunoglobulin, TNF-α antibody (infliximab), rituximab.

*Dose reduction is necessary in patients showing impaired renal function.
#Early plasma exchange is recommended for patients who are dialysis dependent at presentation or biopsy shows severe histological changes (> 50% crescents).
Abbreviation: TNF, tumor necrosis factor.

failure at presentation, promptness of intervention and underlying diagnosis. The potential for recovery corresponds with the relative proportion of cellular or fibrous components in the crescents, and extent of tubulointerstitial scarring and fibrosis.

IN A NUTSHELL

1. Rapidly progressive glomerulonephritis is an acute illness with rapid loss of renal function over days to weeks, characterized histologically by crescentic GN.
2. Prompt diagnosis and early treatment is essential to ensure renal recovery.
3. Treatment strategies should be individualized for patients using standard guidelines.

MORE ON THIS TOPIC

Bagga A, Menon S. Rapidly progressive glomerulonephritis. In: Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008. pp. 319-27.

Sinha A, Puri K, Hari P, et al. Etiology and outcome of crescentic glomerulonephritis. Indian Pediatr. 2013;50:283-8.

IMMUNOGLOBULIN A NEPHROPATHY

Manisha Sahay

Immunoglobulin A (IgA) nephropathy is a common GN with peak incidence in the 2nd and 3rd decades of life. Certain bacterial and viral infections are implicated in the pathogenesis of IgA deposition but the evidence is inconclusive. Genetic factors are suggested to play a role in causation and progression of disease; in some cases the illness is transmitted as an autosomal dominant trait with incomplete penetrance.

The IgA nephropathy is associated with mesangial deposition of predominantly polymeric IgA1. This subclass of IgA carries distinctive O-linked sugars at its hinge region, is chiefly produced in the bone marrow and cleared by liver through sialoglycoprotein receptors and Kupffer cell Fcα receptors. The other subclass, IgA2 has no hinge, does not carry sugars and is chiefly derived from the gastrointestinal and respiratory tract mucosa. Circulating IgA1 in IgA nephropathy has abnormal O-linked hinge region sugars with reduced galactosylation, and is not cleared by the liver. Some patients show increased serum levels of IgA and circulating macromolecular IgA, IgA immune complexes and IgA rheumatoid factor. Mesangial deposition of polymeric IgA1 leads to mesangioproliferative GN. Some patients show activation of the alternate complement pathway with C3 and properdin deposition.

CLINICAL FEATURES

Over one-half of children present with one or recurrent episodes of gross hematuria following upper respiratory infection (synpharyngitic hematuria); some have incidentally detected microscopic hematuria and mild proteinuria. Less than 10% present with nephrotic syndrome or RPGN with edema, hypertension, renal insufficiency and hematuria. Patients with rheumatic diseases, dermatitis herpetiformis, cirrhosis, celiac disease, human immunodeficiency virus (HIV), sarcoidosis and malignancy may also show glomerular deposits of IgA.

DIAGNOSIS

The diagnosis of IgA nephropathy is made on kidney biopsy, performed chiefly for persistent microscopic hematuria and proteinuria, nephrotic syndrome or RPGN. Light microscopy shows focal or diffuse mesangial proliferation and matrix expansion. Segmental crescents and/or necrosis are noted in children with deteriorating renal function. The presence of glomerulosclerosis indicates chronicity. The Oxford histological classification incorporates scores for mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, and tubular atrophy and interstitial fibrosis. Immunofluorescence shows prominent deposits of IgA with or without C3 and IgG in the mesangium and glomerular capillary wall. This IgA is predominantly J chain containing polymeric IgA1; however, mesangial secretory IgA2 may be seen **(Fig. 1D)**. Electron microscopy reveals electron-dense deposits in mesangium, subendothelial and subepithelial spaces.

MANAGEMENT

Patients with biopsy proven IgA nephropathy should be screened for disorders associated with IgA deposits. General interventions consist of measures to slow progression of renal disease, including management of hypertension and proteinuria. ACE inhibitors and angiotensin receptor blockers are preferred because of antiproteinuric and antihypertensive effects **(Box 5)**. The role of fish oil is controversial. Patients with persistent proteinuria despite ACE inhibition and those presenting with nephrotic syndrome may benefit from additional therapy with prednisolone (0.5–1.0 mg/kg/day for 6–12 months). Those with RPGN benefit from combined therapy with IV methylprednisolone 15 mg/kg/day for 3 days, and cyclophosphamide 500 mg/m^2 IV q3–4 weeks for six doses; these patients require prolonged maintenance therapy as for crescentic
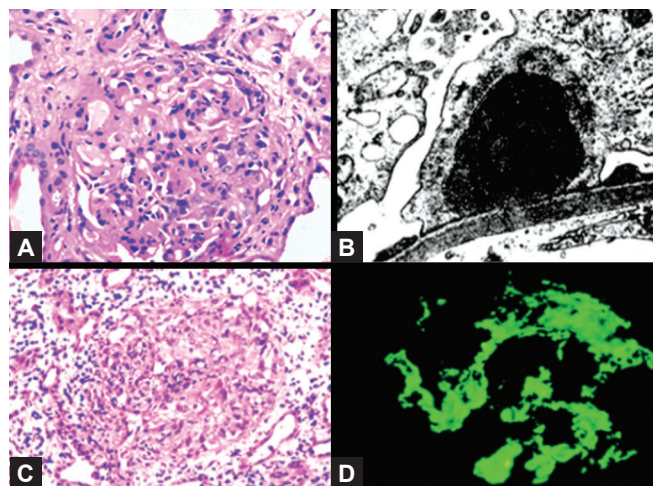
Figures 1A to D (A) Postinfectious glomerulonephritis (GN), showing hypercellular glomerulus with diffuse endocapillary proliferation and infiltration by polymorphonuclear cells; (B) Poststreptococcal GN. Electron microscopy showing a subepithelial electron-dense deposit; (C) Crescentic GN. Note the large circumferential cellular crescent occupying the whole Bowman space. The glomerulus is compressed and shifted; (D) IgA nephropathy. Immunofluorescence examination showing mesangial deposits of IgA1

BOX 5 Treatment of IgA nephropathy (IgAN)

Proteinuria < 1 g/day, blood pressure treatment maintain 130/80 mm Hg in patients with ACEi/ARB

Proteinuria > 1 g/day.

- Blood pressure treatment goals should be 125/75 mm Hg (not graded).
- KDIGO recommends long-term ACE-I or ARB treatment when proteinuria is > 1 g/day, with up-titration of the drug depending on blood pressure.
- KDIGO suggests ACE-I or ARB treatment, if proteinuria is between 0.5 and 1 g/day (in children, between 0.5 and 1g/day per 1.73 m^2).
- KDIGO suggests that patients with persistent proteinuria > 1 g/day, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR > 50 mL/min per 1.73 m^2, receive a 6-month course of corticosteriod therapy.
- KDIGO suggests the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria < 1 g/day.
- KDIGO suggests using fish oil in the treatment of IgAN with persistent proteinuria > 1 g/day, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control).

Nephrotic syndrome

- KDIGO recommends treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy.

RPRF/Crescentic GN

- KDIGO suggests treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients with crescentic IgAN with rapidly deteriorating kidney function analogous to the treatment of ANCA vasculitis.
- KDIGO suggests not using immunosuppressive therapy in patients with GFR < 30 mL/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function.
- KDIGO suggests not using MMF in IgAN.
- Antiplatelet therapy and tonsillectomy are not recommended.

Repeat kidney biopsy in IgAN patients

- AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (Not Graded)
- Kidney biopsy performed during an episode of macroscopic hematuria shows only ATN and intratubular erythrocyte casts hence not advised.

GN (see above). The role of tonsillectomy, plasmapheresis, and combined therapy with heparin, warfarin and dipyridamole is unclear.

Serial monitoring of urine sediment, serum creatinine and protein excretion is recommended. While IgA nephropathy usually has a benign course, progression to ESRD is noted in approximately 20% at 10 years and 30% at 20 years. The presence of elevated serum creatinine, hypertension and nephrotic range proteinuria predict adverse prognosis; obesity, hypertriglyceridemia and hyperuricemia may hasten progression.

Patients with ESRD require dialysis or transplantation. Living-related transplant is not contraindicated. Recurrent IgA deposition in allograft is common (50%), but graft loss is rare. The risk of recurrence increases with living donor, certain human leukocyte antigen (HLA) alleles and high serum IgA. Recurrent IgA nephropathy is managed as disease in native kidneys.

IN A NUTSHELL

1. IgA nephropathy is a common primary glomerular disease characterized by mesangial IgA1 deposits.
2. Patients present with recurrent, synpharyngitic gross hematuria or asymptomatic hematuria and proteinuria. Nephrotic syndrome and crescentic GN are uncommon.
3. Management of hypertension and proteinuria, usually with ACE inhibitors, retards progression of the illness. Corticosteroids are indicated if nephrotic syndrome is present or proteinuria persists despite therapy with ACE inhibitors.

MORE ON THIS TOPIC

Bagga A, Sinha A, Gulati A. IgA nephropathy. In: Protocols in Pediatric Nephrology. New Delhi: CBS Publishers; 2011.

Feehally J, Floege J. IgA nephropathy and HSP nephritis. In: Floege J, Johnson RJ, Feehally J. Comprehensive Clinical Nephrology. 4th ed. Missouri: Saunders-Elsevier; 2010. pp. 288-99.

Hogg RJ. IgA nephropathy: what's new? Pediatr Nephrol. 2007;22:1809-14.

Novak J, Julian BA. Immunoglobulin A nephropathy and Henoch-Schönlein purpura. In: Coffman TM, Falk RJ, Molitoris BA, Neilson EG, Schrier RW. Schrier's Diseases of the Kidney. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2013. pp. 1364-79.

Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines—application to the individual patient. Kidney Int. 2012;82:840-56.

Chapter 41.7
Systemic Vasculitis and Lupus Nephritis
Ashima Gulati, Arvind Bagga

Systemic vasculitides comprise heterogeneous disorders with multiorgan involvement and variable clinical presentation. These conditions may involve small (capillaries and venules), medium arteries (renal, hepatic, mesenteric and coronary) or larger vessels (aorta and large branches) and are classified by the smallest vessel affected in a particular condition. Kidney is among the target organs frequently affected in vasculitis and its involvement is a principal cause of morbidity. Based on the clinical, laboratory and pathological features, distinction between various vasculitic disorders and characterization of disease course is usually possible. Prompt recognition by general pediatricians and early subspecialty referrals are necessary.

EPIDEMIOLOGY AND ETIOPATHOGENESIS

The annual incidence of primary vasculitis in children is approximately 20 per 100,000 population. Ethnicity has an influence on the prevalence, disease manifestations and outcome. Asian children have a higher incidence of lupus and a propensity toward a more severe disease than those of European descent. Kawasaki disease and Takayasu arteritis are more common among Asians. Genetic, environmental and immunological factors act in combination to influence disease susceptibility and pathogenesis *via* generation of autoantibodies, immune complexes, inflammatory T-cells and cytokines that initiate inflammatory damage to various organs. Antecedent infections, especially streptococcal, are implicated in many vasculitides including Henoch-Schönlein purpura (HSP), granulomatosis with polyangiitis and polyarteritis nodosa.

PATHOLOGY

Takayasu arteritis is a large vessel vasculitis characterized by focal granulomatous inflammation with multinucleated giant cells, which progress to fibrosis and vascular narrowing. Polyarteritis nodosa and Kawasaki disease have a predilection for renal and coronary arteries, respectively with focal necrotizing vasculitis and inflammatory aneurysms. The presence of arteritis and glomerulonephritis (GN) indicates small vessel vasculitis. Leukocytoclastic vasculitis in HSP and hypersensitivity vasculitis is characterized by neutrophilic inflammation, scattered nuclear debris (leukocytoclasia) and necrosis of small sized vessels. Renal histology shows focal segmental proliferative GN with or without crescent formation.

CLINICAL FEATURES

The presentation of systemic vasculitides is varied and depends on the size, site and extent of vascular involvement. Recognition of these conditions can be challenging as symptoms may be nonspecific with fever, malaise, diffuse pains; however, with evolving vascular damage more obvious and specific features develop, such as purpuric rash and evidence of organ involvement like GN. Detailed history and examination are critical, with emphasis on recent illnesses, drug exposures, family history, evidence of skin rash, four-limb blood pressure, palpation of peripheral pulses and auscultation for bruit over carotid, axillary,

aortic and renal vessels. Neurological examination is useful to rule out peripheral neuropathy and retinal vascular abnormality.

DIAGNOSIS

Blood investigations should include complete blood counts and acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) to detect systemic inflammation. Other useful tests include kidney and liver function tests, urinalysis (to detect glomerular involvement), antinuclear and antineutrophil cytoplasmic antibodies (ANA, ANCA) and complement factors C3 and C4. Imaging (CT or MR angiography, conventional angiography) detects vessel abnormalities, especially in suspected medium or large vessel disease. Patients with severe renal involvement may require kidney biopsy.

CLASSIFICATION

A classification of major childhood vasculitides, based on the size of the affected vessel, is shown in **Table 1**. **Table 2** summarizes the classification criteria for major vasculitides.

SMALL VESSEL VASCULITIS

Henoch-Schönlein Purpura

Henoch-Schönlein purpura or anaphylactoid purpura accounts for about half of all systemic vasculitides. It is a leukocytoclastic vasculitis affecting children between 3-year-old and 10-year-old. Predilection for winter and spring and antecedent upper respiratory infections suggests an infectious trigger; pathogens implicated include Group A β-hemolytic *Streptococcus*, *S. aureus*, viruses (influenza, parainfluenza, Epstein-Barr, adenovirus, parvovirus) and mycoplasma. IgA-dominant immune deposits are found in small vessels.

Clinical features Henoch-Schönlein purpura is characterized by nonthrombocytopenic purpura, arthritis or arthralgia, abdominal pain and renal involvement. Purpuric rash appears on the

Table 1 Classification of childhood vasculitis

Predominantly large vessel vasculitis
• Takayasu arteritis
Predominantly medium-sized vessel vasculitis
• Childhood polyarteritis nodosa • Cutaneous polyarteritis • Kawasaki disease
Predominantly small vessel vasculitis

• *Granulomatous*
  – Wegener's granulomatosis
  – Churg-Strauss syndrome
• *Nongranulomatous*
  – Henoch-Schönlein purpura
  – Microscopic polyangiitis
  – Hypocomplementemic urticarial vasculitis
  – Isolated cutaneous leukocytoclastic vasculitis

Other vasculitides
• Behçet disease • Vasculitis associated with connective tissue diseases • Isolated vasculitis of central nervous system • Secondary to infection (hepatitis B associated PAN), malignancy and drugs, including hypersensitivity vasculitis • Cogan syndrome • Unclassified

extensor surface of legs and gluteal region but may be seen on the arms and face. The rash may be maculopapular or urticarial but soon becomes purpuric and gradually disappears over 2 weeks. Arthralgia or arthritis affects large joints, is usually oligoarticular and self-limited. Gastrointestinal manifestations may include abdominal pain, bleeding and intussusception. Renal involvement occurs in about one-third of patients within the first 4–6 weeks and almost always within 6 months. Isolated microscopic hematuria with or without proteinuria is the most common; however, children may present with nephritic or nephrotic syndrome, or rarely renal failure. Risk factors for renal involvement are an older age of onset, rash lasting for more than 1 month and severe abdominal symptoms. Atypical presentations include pulmonary hemorrhage, seizures, stroke and mental status changes.

Diagnosis Classification criteria are outlined in **Table 2**. In cases of purpura with atypical distribution, demonstration of leukocytoclastic vasculitis with IgA is required at biopsy performed at the edge of a fresh cutaneous lesion. Kidney biopsy is indicated in presence of significant proteinuria, nephrotic or nephritic syndrome and renal insufficiency.

Table 2 EULAR classification criteria for major childhood vasculitides

Henoch-Schönlein purpura	*Mandatory criterion*: Purpura or petechiae (not related to thrombocytopenia) with lower limb predominance and at least *one* of the following: *(i) Acute abdominal pain:* May include intussusception/gastrointestinal bleeding; *(ii) Histopathology:* Leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits; *(iii) Arthritis or arthralgia of acute onset*; *(iv) Renal involvement**
Polyarteritis nodosa	*Mandatory criterion*: *Angiographic abnormalities,* e.g., aneurysm, stenosis or occlusion, and *histopathology* showing necrotizing vasculitis of medium or small-sized artery, plus one of the following: *(i) Skin involvement*: Livedo reticularis, nodules, ischemic changes; *(ii) Myalgia/muscle tenderness*; *(iii) Hypertension*; *(iv) Peripheral neuropathy*; *(v) Renal involvement**
Wegener's granulomatosis	Presence of at least three of the following: *(i) Histopathology:* Granulomatous inflammation within vessel wall or in perivascular or extravascular area; *(ii) Upper airway involvement:* Chronic purulent or bloody nasal discharge or nasal septal perforation or chronic sinusitis; *(iii) Laryngotracheal bronchial stenosis*; *(iv) Pulmonary involvement:* Chest X-ray or CT findings of nodules, cavities or infiltrates; *(v) ANCA positivity* by immunofluorescence or ELISA; *(vi) Renal involvement**
Takayasu arteritis	*Mandatory criterion*: *Angiographic abnormalities*: aneurysm/dilatation of the aorta or its main branches and one of the following: *(i) Pulse deficit or claudication or four limbs blood pressure discrepancy* (> 10 mm Hg systolic blood pressure difference in any limb); *(ii) Bruit* over large arteries; *(iii) Hypertension*; *(iv) Acute phase reactant*: High erythrocyte sedimentation rate or C-reactive protein

Ozen S, Pistorio A, Lusan SM, *et al*. EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69:798-806.
*Proteinuria (> 0.3 g/24 hours or > 30 mmol/mg of urine albumin/creatinine ratio on spot morning sample or ≥ 2 + on dipstick) or hematuria (> 5 red blood cells/high power field or red blood cells casts in urinary sediment) or impaired renal function (estimated GFR < 50% normal).
Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ELISA, enzyme-linked immunosorbent assay; GFR, glomerular filtration rate.

Treatment Management comprises symptomatic treatment with rest and analgesia for joint pains. Administration of corticosteroids does not prevent HSP nephritis. Indications for systemic steroids include severe gastrointestinal manifestations, orchitis and severe renal involvement. Prednisolone is administered at a dose of 1–2 mg/kg/day for a week, followed by gradual reduction of the dose over 2–3 weeks. Renal disease is mild in the majority and does not require specific therapy. It is recommended that children with HSP nephritis and persistent proteinuria be treated with angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB). Children with persistent proteinuria after a trial of ACE-I or ARBs may be offered a 6-month course of corticosteroid therapy. Children presenting with severe nephritis or nephrotic syndrome are treated with corticosteroids and cytotoxic drugs. Treatment of crescentic GN consists of IV corticosteroids, cyclophosphamide and, in nonresponsive cases, plasma exchange.

Outcome Renal involvement, though self-limited, may be severe, particularly when glomerular crescents are present and can lead to end stage kidney disease in less than 1%. Persistent heavy proteinuria, hypertension and azotemia and with crescents on biopsy indicate a poor prognosis. Approximately 15–40% of patients have at least one recurrence that most commonly consists of rash and abdominal pain, each episode usually being similar but briefer and milder than the preceding one.

Antineutrophil Cytoplasmic Antibody-associated Vasculitides

The ANCA-associated vasculitides includes three classic vasculitides: microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's granulomatosis) and Churg-Strauss syndrome.

Microscopic Polyangiitis

Microscopic polyangiitis is a necrotizing vasculitis of small vessels with few or no immune deposits. It differs from classic polyarteritis nodosa by the presence of extensive glomerular involvement. It usually presents with renal impairment associated with proteinuria, hematuria and hypertension. Malaise, fever, anorexia and weight loss are common; occasionally rashes, arthralgia, myalgia and pulmonary hemorrhage may occur.

Antibodies directed against neutrophil cytoplasmic antigens (ANCA) might be found in patients with microscopic polyarteritis. These antibodies are also associated with Wegener's granulomatosis and other vasculitis limited to kidney. An indirect immunofluorescence assay differentiates two patterns of staining. Diffuse granular staining throughout the neutrophil cytoplasm, termed cytoplasmic (cANCA), corresponds to specificity for proteinase 3 (PR3), and is strongly associated with Wegener's granulomatosis. Concentration of fluorescence around the nucleus, known as perinuclear (pANCA), is usually associated with antibodies against myeloperoxidase (MPO). For diagnostic accuracy, testing for ANCA should also include ELISA for antigen specificity (PR3 or MPO). Approximately 80–85% patients with microscopic polyangiitis have either pANCA or cANCA, the majority having the former.

Renal biopsy shows focal, segmental necrotizing GN with fibrinoid necrosis, thrombosis of glomerular tuft segments surrounded by neutrophils. There may be extensive crescent formation and glomerular immune deposits are scarce or absent, hence the term pauci-immune crescentic GN.

Wegener's Granulomatosis

Wegener's granulomatosis or granulomatosis with polyangiitis causes granulomatous inflammation of the respiratory tract, with necrotizing vasculitis affecting small to medium-sized vessels and necrotizing GN **(Table 2)**.

Treatment of ANCA-associated Vasculitis

The management of ANCA-associated vasculitis consists of immunosuppression in two phases, induction and maintenance. Standard induction therapy includes corticosteroids and cyclophosphamide. Recent studies have examined the role of biologic medications and plasmapheresis as adjunct therapy. Maintenance therapy is using mycophenolate mofetil or azathioprine for 18–24 months. Rituximab (375 mg/m^2/week for 4 weeks), and intravenous immunoglobulin (IVIG) (2 g/kg/month) are options for refractory disease. For details on management, see chapter 41.6.

MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

Childhood polyarteritis nodosa is a necrotizing vasculitis associated with aneurysmal nodules along walls of medium-sized muscular arteries in skin, joints, peripheral nerves, gastrointestinal tract and other organs. It is the third most common childhood vasculitides after HSP and Kawasaki disease. Age of onset ranges from 9 years to 11 years and the overall disease course is associated with fewer relapses and improved survival compared to adult-onset disease. Clinical features relate to vascular insufficiency, mostly in the skin, muscles, kidneys, and gastrointestinal tract. Involvement of the heart, peripheral and central nervous systems are less common and lungs are typically spared. Presentation usually includes malaise, fever, weight loss, abdominal pain, myalgia and arthralgia. Renal involvement, reported in 50–60%, manifests as hematuria and hypertension. In addition, testicular pain, neurological features such as focal deficits, hemiplegia, visual loss, mononeuritis multiplex and ischemic heart disease may occur. Rupture of arterial aneurysms may cause massive intra-abdominal hemorrhage. Painful subcutaneous nodules along affected vessels are a characteristic feature.

Laboratory investigations show anemia, raised ESR and thrombocytosis. Hepatitis B surface antigen is detected in few patients. Vasculitis can be confirmed on biopsy of involved muscle. Renal and hepatic angiography show irregularity, stenosis or occlusion of involved vessels; arterial aneurysms affecting the renal, mesenteric or coronary arteries are suggestive, but not specific for polyarteritis nodosa.

Initial treatment comprises corticosteroids alone or cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine. Plasmapheresis is indicated for severe organ damage. More recently, biologic agents such as rituximab have been used. Addition of antiplatelet drugs is recommended for patients with ischemia. Once controlled, the disease is self-limiting; early withdrawal of therapy may lead to relapses. The prognosis is variable with mortality ranging from 10% to 20% despite aggressive therapy.

LARGE VESSEL VASCULITIS

Takayasu Arteritis (Nonspecific Aortoarteritis)

Takayasu arteritis is a granulomatous vasculitis that affects the aorta and major branches, most commonly the renal, subclavian and carotid arteries. It is a common cause of renovascular hypertension in children in India and Asia. Detection of angiographic abnormalities (conventional, CT or MR) of the aorta or its main branches is a mandatory criterion **(Table 2)**. The early phase of the disease is characterized by systemic features (fever, anorexia, weight loss, cough, joint pains and anemia) that often go unrecognized. Features of renovascular hypertension and hypertensive complications (heart failure) develop subsequently. Patients may have claudicating pain in the extremities, absent pulses and bruits.

Though conventional angiography demonstrating stenosis or occlusion of involved vessels is the gold standard for imaging, it is invasive and cannot detect thickened vessel walls, an early sign of inflammation. CT and MR angiogram show vessel wall thickening.

Treatment consists of tapering doses of corticosteroids when the disease is detected during the acute phase. Patients with severe disease benefit from cytotoxic agents. Hypertension needs to be controlled using appropriate medications. Once the inflammatory phase is passed and stenosis has developed, reconstructive vascular surgery or balloon angioplasty with or without stenting is often required.

LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by widespread inflammation of connective tissues affecting the skin, joints, kidneys, heart, lungs and nervous system. Although commonly diagnosed in women during the second to fourth decades of life, disease onset is in childhood in 15–20%. Biopsy proven lupus nephritis, seen in 60–80% cases of childhood-onset SLE, is among the most common secondary glomerular diseases in childhood and is an important determinant of prognosis.

Clinical Features

Clinical presentation in children may be nonspecific. There is a higher frequency of malar rash, mucocutaneous involvement, renal involvement, seizures, fever, hemolytic anemia, thrombocytopenia and lymphadenopathy; Raynaud phenomenon, pleuritis and sicca symptoms are less common. Renal manifestations are present in almost one-half with presentations ranging from minor urinary abnormalities to severe renal insufficiency. Proteinuria, microscopic or macroscopic hematuria is common. Deranged renal function at onset is seen in 50% children with about 2% requiring renal replacement therapy. A small proportion present with a rapidly progressive GN with biopsy-proven crescentic GN. Hypertension is seen in 40% cases. Patients are at risk of arterial and venous thrombosis.

Evaluation

Investigations that help in disease evaluation and determining its severity include complete blood counts, erythrocyte sedimentation rate, C-reactive protein, renal and liver function tests and electrolytes; urine microscopy, spot protein to creatinine ratio or a 24 hours protein and creatinine excretion. Serological tests include complement C3, C4, antinuclear antibody (positive in 95% by ELISA; usually a homogenous diffuse pattern on immunofluorescence and a peripheral pattern with active disease), antidouble stranded DNA (specific for SLE; presence of high titers is related with active lupus nephritis), anti-Smith (specific to SLE and proposed to be a marker of central nervous system disease), antiphospholipid antibodies (anticardiolipin antibodies, IgG and IgM, and lupus anticoagulant; should be examined in recurrent thrombosis, livedo reticularis, chorea, cerebrovascular accidents and hypertension), anti-Ro, anti-La and antiribonucleoprotein.

Renal Histology

Kidney biopsy is required for determining prognosis and defining treatment. The WHO classification of lupus nephritis is widely accepted. A revised classification proposed by the International Society of Nephrology and Renal Pathologic Society emphasizes the utility of activity and chronicity indices while reporting biopsy specimens and standardizes definitions to encourage uniform and reproducible reporting **(Table 3)**.

Table 3 Histological classification of lupus nephritis proposed by the International Society of Nephrology Renal Pathology Society

Class	Nomenclature	Description
I	Minimal mesangial lupus nephritis	Normal appearing glomeruli by light microscopy (LM) with immune deposits confined to the mesangium by immunofluorescence (IF) or by IF and electron microscopy (EM)
II	Mesangial proliferative lupus nephritis	Mesangial proliferation by LM and mesangial deposits by IF; isolated small immune deposits by IF or EM involving the peripheral capillary walls may be present. Any subendothelial deposits by LM qualify as class III or IV
III	Focal lupus nephritis[*] (< 50% of glomeruli): active (A), active and chronic (A/C) or chronic (C) lesions	Focal lupus nephritis involving < 50% glomeruli; glomeruli display segmental endocapillary proliferative lesions, with or without capillary wall necrosis and crescent, with subendothelial deposits
IV	Diffuse lupus nephritis[**] (≥ 50% of glomeruli): Segmental (S) or global (G) lesions; (A)/(A/C)/(C)	Involvement of 50% or more glomeruli in the biopsy; lesions may be segmental or global
V[£]	Membranous lupus nephritis	Membranous lesion with global or segmental continuous granular subepithelial immune deposits with any degree of mesangial hypercellularity. Any subendothelial deposits by LM warrant a combined diagnosis of class III and V or class IV and V; however, scattered subendothelial immune deposits may be identified by IF or EM
VI	Advanced sclerosing lupus nephritis	Includes biopsies with > 90% global glomerulosclerosis with clinical or pathologic evidence of sclerosis being attributable to lupus nephritis

[*]Indicate the proportion of glomeruli with active and with sclerotic lesions.
[**]Indicate the proportion of glomeruli with fibrinoid necrosis and with cellular crescents.
[£]Diagnosis of combined class III/IV and V requires membranous involvement of at least 50% of the glomerular capillary surface area of at least 50% of glomeruli by light microscopy or immunofluorescence.

Treatment

The treatment of SLE depends on severity of the disease. No specific therapy is necessary for milder forms of lupus nephritis (class I). Such patients require management of the extrarenal manifestations and should be under regular surveillance for exacerbation of the disease. In moderate to severe active nephritis (class III and IV), treatment with high-dose oral steroids and cytotoxic drugs is indicated. Prednisolone is initially given at a dose of 1–2 mg/kg daily for 4–6 weeks and then gradually tapered to a maintenance dose of 0.2–0.3 mg/kg daily, for 2–3 years or more. Patients with class III and IV lupus nephritis are also given cyclophosphamide, preferably IV every 3–4 weeks for 6–7 pulses, or orally (2 mg/kg daily for 3–4 months). Subsequently, cyclophosphamide is replaced either by azathioprine (1–2 mg/kg per day) or mycophenolate mofetil. Patients with class V nephritis may be treated with a combination of oral prednisolone and either a calcineurin inhibitor (*e.g.,* cyclosporine) or mycophenolate mofetil. In patients with rapidly progressive renal failure or those showing sudden deterioration of renal function, 3–6 doses of IV pulse methylprednisolone (500–750 mg/m^2) may be used before administering oral corticosteroids.

Rituximab, a chimeric monoclonal antibody directed against the CD20 cell-surface receptor expressed on immature, mature and activated B-cells, is increasingly used in multiple autoimmune disorders. Rituximab may have a beneficial role in patients with severe active lupus nephritis. It is presently used to treat SLE resistant to standard mediations. Plasma exchange and IV immunoglobulin be useful in similar situations.

Prognosis

Childhood-onset lupus nephritis carries a worse renal prognosis compared with adults. Relapses of lupus nephritis occur in approximately one-third of treated patients and are associated with worsened kidney outcomes, such as doubling of serum creatinine and a higher risk for end-stage renal disease. However, mortality from renal failure is lower with increasing use of effective therapies. Kidney transplantation in patients with lupus nephritis has similar long-term patient and graft survival when matched to controls, with less than 10% risk of disease recurrence and a nonsignificant trend toward higher infection-associated mortality.

IN A NUTSHELL

1. The size, site, and extent of vessel involvement determine presentation and severity of childhood vasculitides. Newer validated classification criteria enable identification of disease course and expected severity.
2. Early diagnosis and prompt treatment may improve outcomes. Management involves a multidisciplinary team approach and long-term follow-up.
3. Manifestations of lupus nephritis are severe in children; adequate immunosuppression is necessary, but needs to be balanced with side effects of these medications.

MORE ON THIS TOPIC

Chartapisak W, Opastirakul S, Hodson EM, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein Purpura. Cochrane Database Syst Rev. 2009;3:CD005128.

KDIGO Clinical practice guidelines for glomerulonephritis. Kidney International Supplements. 2012;2:142.

Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69:798-806.

Chapter 41.8
Alport Syndrome and Related Disorders
Mukta Mantan

Alport syndrome and thin basement membrane nephropathy (TBMN) are genetic diseases of the glomerular basement membrane involving the $\alpha3/\alpha4/\alpha5$ network of type IV collagen. Alport syndrome is an inherited progressive disease that presents typically with hematuria in childhood with progressive proteinuria and renal impairment in later years. Males with mutations in the X-linked *COL4A5* gene show progressive renal and sometimes extrarenal disease. Females who are heterozygous for a *COL4A5* mutation are carriers for the condition. TBMN is an autosomal dominant disorder characterized by microscopic glomerular hematuria, minimal or no proteinuria and normal renal function. It is often diagnosed incidentally and has an excellent prognosis.

ALPORT SYNDROME

The prevalence of Alport syndrome varies from 1 in 5,000–50,000 individuals and accounts for 1–2% population with end stage renal disease in the developed world; data from developing countries is limited.

Pathogenesis

The basement membrane of the glomerulus is formed by interweaving of type IV collagen with laminins, nidogen and sulfated proteoglycans. The type IV collagen family of proteins comprises six isomeric chains, designated as $\alpha1$ (IV) to $\alpha6$ (IV). These chains show extensive sequence homology and share basic structural features. Each type IV collagen molecule is a heterotrimer composed of three α chains. The genes *COL4A1* to *COL4A6* encoding the six-chains of collagen IV-$\alpha1$ (IV) through $\alpha6$ (IV) are expressed in different membranes at various steps of embryonic development. The embryonic kidney contains $\alpha1\alpha1\alpha2$ collagen IV protomers while in normal, mature kidney collagen $\alpha3\alpha4\alpha5$ (IV) trimers are found in glomerular basement membrane, Bowman capsule and basement membrane of distal tubules; these timers are also found on ocular and cochlear basement membranes. The $\alpha3\alpha4\alpha5$ protomer has multiple disulfide bonds rendering it resistant to proteolysis and conferring mechanical strength. Mutations in *COL4A3*, *COL4A4* or *COL4A5*, the genes encoding $\alpha3$, $\alpha4$ and $\alpha5$ chains result in incorrect formation of collagen IV protomers that are degraded allowing a persistence of the embryonic network of the basement membrane, which becomes weak with time. A compensatory overproduction of atypical laminin isoforms (laminin $\alpha1$ and $\alpha5$) and the altered type IV collagen contribute to increased permeability of the basement membrane and production of transforming growth factor (TGF$\beta1$) resulting in glomerulopathy and fibrosis.

Genetics

Of three genetic forms of Alport syndrome, the X-linked form is the most common (85% patients) and is caused by mutations in *COL4A5* gene. Males afflicted with the condition are hemizygotes carrying a single mutant gene while females are heterozygotes with one normal and other mutant gene and are mostly carriers. All affected males progress to renal failure; the course is usually benign in females. The recessive form of the disease occurs in 10–15% patients due to mutations in both alleles of *COL4A3* or *COL4A4* gene located at chromosome 2q35-37. Heterozygous mutations in these genes results in autosomal dominant form of disease that occurs in 5% subjects. Most patients with dominant disease are asymptomatic or present with isolated hematuria that is nonprogressive.

Genetic testing for Alport syndrome is limited to a few laboratories worldwide. More than 200 mutations have been identified in *COL4A3* and *COL4A4* genes. The spectrum of mutations is broad and provides insight into the heterogeneity of Alport syndrome with respect to age at renal failure and features such as deafness, leiomyomatosis and antiglomerular basement membrane (anti-GBM) nephritis. The identification of variants of the *COL4A5* gene helps in confirming the diagnosis and understanding the prognosis.

Clinical Features

Renal manifestations begin as hematuria that later progress to proteinuria and end stage renal disease. Pedigrees with the disease vary in rapidity of onset of renal failure. Patients with nonsense or missense, frame shift mutations or large deletions in their chromosomes develop end stage renal disease by 30 years of age while individuals with splice variants or exon-skipping mutations show renal failure after 30 year of age. Sensorineural hearing loss progressively develops in late childhood, in 80% afflicted boys and 25–30% girls. The hearing loss plateaus at around 80–90 decibels and some useful hearing always remains; patients improve with hearing aids. The ocular features are primarily an anterior lenticonus; the lens slowly becomes conical in shape and leads to myopia that can be corrected with appropriate lenses. Rarely lens extraction may be required. Macular flecks are white flecks scattered around the macula and also at the periphery; they do not affect vision. Ocular changes occur in 30–40% of males with X-linked disease and 15% affected females.

The association of leiomyomatosis (smooth muscle tumors) of the esophagus and the tracheobronchial tree is reported in 20–30 families, in association with deletions involving *COL4A5* and *COL4A6* genes. Symptoms appear in late childhood and include dysphagia, vomiting, epigastric pain, cough, stridor and recurrent bronchitis.

Diagnosis

Alport syndrome should be suspected in patients (especially males) with persistent glomerular microscopic hematuria once structural abnormalities of the kidney and urinary tract have been ruled out. A positive family history of hematuria or renal failure may suggest the diagnosis. Renal biopsy changes are less marked in children compared to adults. Light microscopy shows variable thickening of the glomerular basement membrane. Electron microscopy shows initial thinning of the glomerular basement membrane, that later changes to basket weaving and lamellation.

On indirect immunofluorescence an absence of $\alpha3$, $\alpha4$ and $\alpha5$ chains of type IV collagen from basement membrane of the glomeruli and the distal tubules helps in diagnosis, since the finding is exclusive to Alport syndrome. Examination of skin biopsies by immunofluorescence for the expression of $\alpha5$ (IV) collagen in the epidermal basement membrane can also identify X-linked condition. However normal expression of type IV collagen α chains does not exclude the diagnosis. Most heterozygote females with the condition would have normal skin biopsies. A firm histological diagnosis of the syndrome is not always possible despite careful study of the pedigree and histopathology.

The diagnosis of Alport syndrome is confirmed if there is a lamellated glomerular basement membrane or a pathogenic mutation in *COL4A5* gene or two pathogenic *COL4A3* or *COL4A4* mutations. Genetic testing has a sensitivity of more than 90%

for the diagnosis of X-linked disease; more than 700 variants are described.

Treatment

The presence of proteinuria, hearing loss, lenticonus, retinopathy and deficient collagen IV α5 chains in glomerular basement membrane in male patients correlate with an increased likelihood of early onset renal failure. The hearing defect improves on use of hearing aid; the myopia due to lenticonus can be corrected. Angiotensin converting enzyme inhibitors reduce proteinuria and delay the onset of renal failure in children with X-linked disease. The additional use of angiotensin receptor blockers and/or aldosterone inhibitors may further reduce proteinuria, but combined therapy should be used cautiously.

Renal replacement therapy may be required when patients reach end stage renal disease. Family renal donors should be carefully screened for Alport syndrome. The outcomes of renal transplantation are excellent. Post-transplant monitoring should include early identification of anti-GBM nephritis that occurs in about 3% of transplanted males.

THIN BASEMENT MEMBRANE NEPHROPATHY

Thin basement membrane nephropathy is an inherited disorder of glomerular basement membrane that is transmitted in an autosomal dominant manner. It affects about 1% of the population. It differs from Alport syndrome in being a more benign condition and does not have any extrarenal manifestations. Familial TBMN has been localized to *COL4A3* or *COL4A4* in some kindreds. Immunohistological studies of type IV collagen in basement membrane of TBMN do not revealed any abnormalities.

Clinical Features

Patients with TBMN usually present with intermittent or persistent microscopic hematuria during childhood. Proteinuria and hypertension are rarely reported. While the disease is non-progressive, the risk of renal failure is increased if there is coincidental renal disease or diabetes.

Histology

Light microscopy and immunofluorescence study do not reveal any specific changes. Electron microscopy shows glomerular basement membrane thinning. While the thickness of the basement membrane in childhood varies between 200 nm and 250 nm, values below 200 nm suggest thinning. The basement membrane is thinned in the majority of capillary loops, and at least 50% of the membrane is thinned in individual capillaries.

Diagnosis

Presence of a family history of hematuria in multiple generations without progression to end stage renal disease suggests the diagnosis. Ophthalmological and ocular examinations help in differentiating from Alport disease. Presence of proteinuria, hypertension, renal dysfunction or other atypical features may necessitate renal biopsy.

Treatment

Most patients have a good prognosis. Careful follow-up every 1–2 years with measurement of blood pressures and kidney function tests is recommended. Rarely patients may show hypertension or significant proteinuria, which should be treated with ACE inhibitors.

OTHER INHERITED CONDITIONS

Pierson Syndrome

Patients with this condition have ocular abnormalities (buphthalmos, microcoria, cataract and retinal abnormalities) in association with congenital nephrotic syndrome. The gene for the condition, *LAMB2* gene, encodes for laminin β2 chains.

Nail-Patella Syndrome

This autosomal dominant disorder is characterized by the presence of dystrophic nails, hypoplastic or absent patella, dysplasia of elbow and iliac horns and renal disease. The gene for the condition is located on chromosome 9q34 (*LMX1B*). Renal disease varies from microscopic hematuria and mild proteinuria to nephrotic syndrome; few patients have hypertension. The risk of progression to end stage renal disease is low (< 10%). Renal biopsy does not show specific findings on light microscopy; electron microscopy reveals moth eaten appearance of the basement membrane.

Fabry Disease

This is an X-linked disorder of glycosphingolipid metabolism, due to deficient enzyme, lysosomal hydrolase α galactosidase A, that results in involvement of kidneys, heart and peripheral and central nervous systems. Patients present in childhood with paresthesias and pain in hands and feet. Angiokeratomas of the skin develop by second decade. Renal involvement is characterized by mild to moderate proteinuria and microscopic hematuria. Nephrotic syndrome is unusual and end stage renal disease develops between third and sixth decades. The diagnosis is confirmed by demonstrating decreased enzyme activity in serum, leukocytes or cultured skin fibroblasts; slit lamp examination shows corneal opacities. The role of recombinant enzyme replacement in preventing or delaying renal failure is being examined.

IN A NUTSHELL

1. Alport syndrome is an X-linked condition where the glomerular basement membrane undergoes progressive thickening. Males with persistent microscopic hematuria should be suspected for the condition and undergo hearing assessment and eye evaluation.
2. Renal biopsy of children with Alport syndrome may be normal on light microscopy; electron microscopy reveals basket weaving of the basement membrane, while indirect immunofluorescence shows absence of α3, α4 and α5 chains of type IV collagen from GBM.
3. Early use of angiotensin converting enzyme inhibitors delays progression of renal failure.
4. Thin basement membrane nephropathy, a close differential of Alport syndrome, occurs with equal frequency in both genders. The outcomes are good and end stage renal disease is rare.

MORE ON THIS TOPIC

International Alport Mutation Consortium, Savige J, Ars E, et al. DNA variant databases improve test accuracy and phenotype prediction in Alport syndrome. Pediatr Nephrol. 2014;29: 971-7.

Noone D, Licht C. An update on the pathomechanisms and future therapies of Alport syndrome. Pediatr Nephrol. 2013;28:1025-36.

Savige J, Gregory M, Gross O, et al. Expert guidelines for the management of Alport syndrome and thin basement membrane disease. J Am Soc Nephrol. 2013;24:364-75.

Chapter 41.9
Proteinuria
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In the healthy state, urine contains minimal protein. The barrier to protein excretion is at the level of glomeruli, where size of protein molecules and their negative charge inhibits glomerular filtration. The minimal protein that passes through into the glomerular filtrate is reabsorbed in the proximal tubule. There is some tubular secretion, in form of low molecular weight proteins (70% being Tamm-Horsfall protein). The normal range of urinary protein excretion in children is less than 4 mg/m^2/hour in a timed urine sample, less than 100 mg/m^2/day, or less than 0.2 (0.5 in infants) mg of protein/mg of creatinine in a spot urine sample. Larger excretion of protein is defined as proteinuria **(Table 1)**.

Any damage causing increase in the pore size or disruption of negative charge of the glomerular basement membrane results in proteinuria which may be selective where mainly albumin is excreted, or nonselective, where proteins of higher molecular weight such as transferrin and IgG are excreted. Proteinuria in such cases exceeds the proximal tubular capacity of reabsorption. Tubular proteinuria, usually of smaller magnitude, occurs when a tubular pathology results in lack of reabsorption of low molecular weight proteins (e.g., beta 2 microglobulin, retinol binding protein). Tubular injury can also lead to release of tubular proteins such as neutrophil gelatinase-associated lipocalin into the urine. Albuminuria is a marker of renal pathology. Subtle glomerular injury may be associated with urinary albumin values between 30 mg/g and 300 mg/g of creatinine (termed microalbuminuria), while greater values indicate more significant disease. These parameters are commonly used for the early detection of renal injury.

Orthostatic proteinuria occurs in the upright position but subsides after rest. This is determined by checking urinary protein excretions after overnight sleep and comparing it with a value obtained later in the day when the patient has been upright for some time. This phenomenon is usually seen in older children and thought to represent physiological changes in renal hemodynamics, and is generally benign in nature. It requires occasional monitoring but no further evaluation. *Exercise-induced proteinuria* occurs during or after exercise but reverts to normal ranges when tested several days later. *Transient proteinuria* occurs with acute diseases such as dehydration, urinary infection, acute kidney injury or febrile illness. It subsides once the acute illness resolves. Patients with persistent proteinuria, that continues for at least 4 weeks and is present in repeated measurements, need evaluation.

Table 1 Definitions: quantification of proteinuria

Terminology	Protein (mg/m^2/hour)	Protein : creatinine ratio (mg/mg)
Proteinuria	≥ 4	≥ 0.2
Nonnephrotic range proteinuria	$\geq 4 - < 40$	$\geq 0.2 - < 2$
Nephrotic range proteinuria	≥ 40	≥ 2

DETECTION OF PROTEINURIA

Proteinuria is detected semiquantitatively using dipstick on an early morning specimen. Heat precipitation or sulfosalicylic acid tests are also useful. For quantitative estimation, the first or second urine specimen, used for ratio of urinary protein to creatinine, has satisfactory correlation with 12- or 24 hours specimens. While cumbersome to obtain, the 24 hours sample is considered standard as it accounts for differences in proteinuria with time and fluid intake.

EPIDEMIOLOGY

Proteinuria may be associated with different physiological and pathological events. A Panel on proteinuria, albuminuria, risk, assessment, detection, and elimination reported that after four tests, 10.7% of children have proteinuria in one of four specimens. However, only 0.1% had positive protein in all specimens.

APPROACH TO A PATIENT WITH PROTEINURIA

Patients with proteinuria require detailed clinical history and evaluation. This is followed by laboratory tests and imaging as indicated. Patients with fever, abdominal lump, oliguria, hematuria, edema, hypertension and fluid overload have significant pathology and require further evaluation **(Table 2)**. Those with *nephrotic syndrome* have nephrotic range proteinuria, hypoalbuminemia, edema and hyperlipidemia. Patients with *glomerulonephritis* show raised urea and creatinine, hypertension and *active urinary sediment* with red cells and casts, and lower degree of proteinuria. Patients with renal or bladder tumors, obstructive uropathy and renal stones may present with pain or abdominal lump. Investigations include urine microscopy and culture, and blood tests for urea, creatinine, electrolytes, albumin and cholesterol. Serological tests such as ASOT, ANA, antidsDNA and ANCA may also be required. Renal imaging is necessary to diagnose structural abnormalities and to differentiate between acute and chronic kidney disease. A renal biopsy is done where the diagnosis is not clear or if histopathological details are required for management.

Asymptomatic proteinuria is detected incidentally. If it persists on repeated examinations including on an early morning sample (to exclude orthostatic and exercise-induced proteinuria), it should be confirmed on a timed urine sample. Family history is taken for conditions like Alport syndrome and polycystic kidney disease. Renal functions are assessed and urinalysis is done for hematuria. Eye examinations and audiometry is required to exclude inherited diseases. Renal ultrasonography and further imaging is done to evaluate for specific conditions.

The presence of significant hematuria or renal dysfunction makes significant pathology likely, and detailed evaluation should follow (as mentioned above). Patients with isolated asymptomatic proteinuria need to be evaluated and monitored over the long-term. A kidney biopsy is necessary in patients showing increasing proteinuria.

MANAGEMENT

Nonspecific reduction of proteinuria has a renoprotective role. Drugs that inhibit the renin-angiotensin system, i.e., angiotensin converting enzyme inhibitors and angiotensin receptor blocker have significant antiproteinuric action. They act by causing vasodilation of the efferent glomerular arteriole and thereby reducing GFR and subsequently protein excretion. These

Table 2 Differential diagnosis of symptomatic proteinuria

Presentation	Clinical features	Differential diagnosis	Investigations
Nephrotic syndrome	Oliguria Edema	Nephrotic syndrome (varied histology)	Creatinine, albumin Cholesterol Renal biopsy
Nephritic syndrome with or without systemic features	Oliguria Hematuria Fluid overload Hypertension Rash, arthritis	Postinfectious GN IgA nephropathy Membranoproliferative GN Hemolytic uremic syndrome Rapidly progressive GN Vasculitides Systemic lupus	Creatinine, ASO, C3 IgA levels Serology for hepatitis B, C; HIV Hemogram, smear; LDH, C3, antinuclear; antineutrophil cytoplasmic antibodies C3, antinuclear antibodies Renal biopsy
Tubular disorder	Polyuria, polydipsia Acidosis Rickets Short stature	Fanconi syndrome Dents disease	Aminoaciduria, β2 microglobulin Serum and urine: electrolytes, calcium, phosphate Venous pH, bicarbonate Genetic studies
Urinary infection, abdominal pain	Dysuria Loin, suprapubic pain Fever Abdominal lump	Urinary infection Stones Polycystic kidneys Obstructive uropathy Tumor	Urinalysis, culture Hemogram, CRP Stone screen Creatinine Renal imaging

Abbreviations: C3, complement 3; GN, glomerulonephritis; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase.

medications should be used under supervision, since they might be associated with reduced GFR and risk of hyperkalemia, especially in volume depleted states.

IN A NUTSHELL

1. Proteinuria is a nonspecific indicator of renal injury.
2. Patients with symptomatic and persistent proteinuria require detailed evaluation.
3. Blockade of the renin angiotensin axis is beneficial in reducing severity of proteinuria and improving outcomes.

MORE ON THIS TOPIC

Bagga A, Sinha A, Gulati A. Protocols in Pediatric Nephrology. New Delhi: CBS Publishers; 2012.pp.5-8.

Fine LG, Salehmoghaddam S. Proteinuria. In: Walker HK, Hall WD, Hurst JW. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston: Butterworths; 1990.

Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: Recommendations from a Pediatric Nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). Pediatrics. 2000;105:1242-9.

Leung AK, Wong AH. Proteinuria in children. Am Fam Physician. 2010;82:645-51.

Chapter 41.10
Nephrotic Syndrome

Arvind Bagga, Aditi Sinha

Nephrotic syndrome, characterized by heavy proteinuria (> 1 g/m², 40 mg/m²/hour or spot urine protein/creatinine > 2), hypoalbuminemia (serum albumin < 2.5 g/dL), hyperlipidemia (serum cholesterol > 200 mg/dL) and edema, is a common chronic kidney disease in children, with an incidence of about 16 per 100,000 children. The disease is idiopathic or primary in more than 90% cases; a secondary cause, *e.g.,* systemic lupus, hepatitis B or C, amyloidosis or Henoch-Schönlein purpura, is uncommon. Response to corticosteroid therapy is the most important determinant of outcome. **Box 1** lists important definitions of disease course. The majority of patients are steroid responsive, with variable disease course but satisfactory outcomes.

PATHOLOGY

In over 80% patients, the histology shows insignificant glomerular abnormalities on light microscopy, termed minimal change disease **(Fig. 1A)**. While immunofluorescence is negative for deposits of immunoglobulins or complement, electron microscopy reveals effacement of podocytes foot processes with disruption and disorganization of actin filaments. A small proportion shows mesangial proliferation (presence of 3–4 cells per mesangial lobule). A small proportion of patients with steroid sensitive nephrotic syndrome have focal segmental glomerulosclerosis (FSGS), with sclerosis involving a segment of the glomerular tuft **(Fig. 1B)**. Collapsing glomerulopathy, a subtype of FSGS, associated with human immunodeficiency virus or parvovirus infection, shows rapid progression to end stage renal disease.

Histology in patients with steroid-resistant nephrotic syndrome shows minimal change disease and FSGS in 30–40% patients each, and mesangioproliferative glomerulonephritis in a small group. About 10–15% patients with steroid resistance show membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, IgA nephropathy or amyloidosis. Some syndromic forms of nephrotic syndrome are associated with diffuse mesangial sclerosis.

PATHOGENESIS

The pathogenesis of minimal change disease remains unclear. Proteinuria results from altered permeability of the glomerular filtration barrier, which comprises the podocyte slit diaphragms, glomerular basement membrane and fenestrated capillary endothelium. Disease relapses often follow minor infections or immunization, and it is proposed that altered cell-mediated immunity possibly associated with T helper 2 immune response causes T-cells to release an uncharacterized circulating factor that increases glomerular permeability. The hypothesis is supported by the disease association with Hodgkin lymphoma, asthma and atopy, response to therapy with agents inhibiting T-cell function, occurrence of remission following measles and lack of inflammation on histology. Proposed circulating factors include interleukin 13, angiopoietin-like-4 and CD80 for minimal change and soluble urokinase plasminogen activator receptor, vascular endothelial growth factor and circulating proteases like hemopexin in FSGS.

Other workers speculate that disease relapses occur when microbial products activate innate immune responses to trigger toll like receptors on podocytes. Proteinuria in experimental models is linked to increased podocyte expression of CD80 (B7-1), a dendrite-associated receptor that mediates co-stimulatory signaling in T-cells. It is proposed that an imbalance of T helper 17 and T regulatory responses perpetuates persistent CD80 activation on podocytes, leading to proteinuria. Further, the ability of rituximab, an anti-B-cell agent, to sustain remission in steroid sensitive disease suggests that B-cell-mediated immune responses are important, including crosstalk between B-cells and T helper

Figures 1A to D Histology in nephrotic syndrome. (A) Minimal change disease. Note that the glomerulus has patent capillaries with normal basement membrane and cellularity; (B) Focal segmental glomerulosclerosis. Note the advanced segmental changes with adhesion to the Bowman's capsule, collapse of the capillary loops and hyalinosis; (C) Membranoproliferative glomerulonephritis. Hypercellularity, thickening of capillary walls and a lobular appearance of the glomerular tuft; (D) Membranous nephropathy. Note the thick glomerular walls with normal mesangial cellularity and patent capillary lumina

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BOX 1 Definitions

Nephrotic range proteinuria: 3 + /4+ (300–1,000 mg/dL) urine protein by dipstick on first morning urine for 3 consecutive days, spot protein/creatinine ratio > 2 mg/mg or urine protein excretion > 40 mg/m²/hour

Remission: Urine protein < 4 mg/m²/hour or nil/trace for three consecutive early morning specimens

Relapse: Urine protein more than 40 mg/m²/hour or 3+ or 4+ for three consecutive early morning specimens, having been in remission previously

Frequent relapses: Two or more relapses within 6 months or four or more relapses in 12 months

Steroid dependence: Two consecutive relapses during corticosteroid therapy or within 14 days of its discontinuation

Steroid resistance: Absence of remission despite therapy with prednisolone at a dose of 2 mg/kg/day for 4 weeks

cells. Another aspect that might have a role in disease pathogenesis is the regulation of actin dynamics, with emphasis on signaling pathways between slit diaphragm and actin cytoskeleton that regulate podocyte morphology and motility.

About 10–25% of patients with sporadic steroid-resistant nephrotic syndrome show mutations in genes encoding key proteins in the slit diaphragm, podocyte cytoskeleton, glomerular basement membrane or mitochondria, or encode transcription factors necessary for normal development. **Table 1** lists genes known to be altered in patients with steroid resistance, particularly familial forms. It is expected that the use of Nextgen sequencing techniques shall lead to further understanding of disease biology in steroid-resistant nephrotic syndrome.

STEROID SENSITIVE NEPHROTIC SYNDROME

Presentation and Initial Evaluation

Patients usually present between 2 years and 5 years of age with insidious onset of edema, first periorbital and subsequently on legs and abdomen. The presence of sustained hypertension, impaired renal function and persistent microscopic hematuria suggest the possibility of significant glomerular lesions. History and physical examination should focus on secondary etiology, prior therapies and evidence of infections.

Suggested evaluations at onset of nephrotic syndrome include: (1) urinalysis for proteinuria, red cells and casts; (2) blood levels of urea, creatinine, albumin, cholesterol; (3) complete blood counts; and (4) tuberculin test. Precise quantitative assessment of proteinuria is not necessary for diagnosis. Depending on clinical and laboratory findings, the following may be required: (1) C3 and antistreptolysin O (if gross or persistent microscopic hematuria); (2) chest X-ray (positive tuberculin test; history of contact with tuberculosis); (3) hepatitis B surface antigen (recent jaundice, elevated transaminases); (4) antinuclear antibodies (suspected systemic lupus); and (5) urine culture (features of urinary tract infection).

Renal Biopsy

A renal biopsy is not required to confirm the diagnosis of minimal change disease before starting treatment. A biopsy is recommended in children with atypical features at onset, including: (1) age less than 1 year or more than 16 years; (2) gross or persistent microscopic hematuria; (3) low blood C3; (4) sustained severe hypertension; (5) impaired renal function not attributed to hypovolemia; and (6) suspected secondary cause. Patients in whom a diagnosis of initial or late steroid resistance is made require renal biopsy to determine the underlying pathology. A renal biopsy is done prior to therapy with calcineurin inhibitors. The specimen is examined by light, immunofluorescence and electron microscopy.

Management of the Initial Episode

The child should receive a high protein diet. Salt is restricted to the amount in usual cooking and salty snacks avoided. Associated infections require treatment. Diuretics are administered only if edema is significant, using them cautiously to avoid overzealous weight loss. Furosemide (1–4 mg/kg/day in two divided doses) alone or with an aldosterone antagonist, spironolactone (2–3 mg/kg/day in two divided doses) is adequate.

Therapy with corticosteroids results in remission of proteinuria, usually by 10–14 days, diuresis and loss of edema. The initial (first) episode of nephrotic syndrome should be treated adequately, both in terms of dose and duration of corticosteroids. Only prednisolone and prednisone are of proven benefit in the treatment of proteinuria. Other agents such as deflazacort, methylprednisolone, dexamethasone, betamethasone, triamcinolone or hydrocortisone should not be used. Prednisolone is administered after meals to reduce gastrointestinal side effects; antacids are not required unless there is gastrointestinal intolerance. Prednisolone is given at a dose of 60 mg/m^2 in single or divided doses for 6 weeks, followed by 40 mg/m^2 as a single morning dose on alternate days for the next 6 weeks. Therapy with corticosteroids is then stopped. Prolongation of initial steroid therapy to 12 weeks is associated

Table 1 Inherited defects in patients with steroid resistant nephrotic syndrome

Gene	Protein	Location	Histology	Phenotype
NPHS1	Nephrin	Slit diaphragm	Microcystic dilatation of tubules; progressive mesangial sclerosis	Congenital nephrotic syndrome
NPHS2	Podocin	Slit diaphragm	FSGS	Congenital nephrotic syndrome; early onset SRNS
CD2AP	CD2-associated protein	Slit diaphragm	FSGS	Adult onset SRNS (heterozygous); early onset FSGS (homozygous)^
TRPC6	Transient receptor potential ion channel 6	Cell surface	FSGS	Adult onset SRNS^
PLCE1/ NPHS3	Phospholipase C epsilon 1	Intracellular	DMS; FSGS	Early onset SRNS
WT1	Wilms' tumor 1	Intracellular	DMS (Denys-Drash); FSGS (Frasier)	Early onset SRNS; Denys-Drash or Frasier syndrome^
ACTN4	α-actinin-4	Intracellular	FSGS	Adult onset SRNS (incomplete penetrance, slow progression); FSGS^
INF2	Inverted formin 2	Intracellular	FSGS	Adult onset SRNS; FSGS^
LMX1B	LIM-homeodomain transcription factor 1β	Intracellular		Nail-patella syndrome; SRNS^
APOL1	Apolipoprotein L1	Intracellular	FSGS	Adult onset SRNS (incomplete penetrance)^
LAMB2	Laminin-β2	Glomerular basement membrane	DMS (syndromic); FSGS (isolated)	Pierson syndrome; early onset SRNS

Abbreviations: DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; SRNS, steroid-resistant nephrotic syndrome; ^AD, autosomal dominant.

with significantly reduced risk for subsequent relapses compared to briefer courses. While a few studies support that tapering the dose of corticosteroids over an additional 8–12 weeks is useful, such prolongation was not shown to be beneficial in recent studies, and requires consideration of the risk of adverse effects.

Parent Education
Parents should be explained about the disease and the usual outcome. They are taught how to examine urine for protein, which is done periodically to detect a relapse. No dietary restrictions are imposed during periods of remission.

Subsequent Course
Around 15–25% patients have only a single episode of the illness, while the majority shows relapses. Infrequent and frequent relapses are noted in 25–40% patients each; 15–20% remains in remission while on therapy and relapse whenever the dose is reduced or within 2 weeks of its discontinuation (steroid dependence). Almost 10% patients either do not respond to initial treatment with prednisolone, or do so transiently and later cease to respond (steroid resistant).

Management of Relapse
Relapses are often triggered by minor infections; therapy of infectious illness might result in remission of 1+/2+ proteinuria. However, persistence of 3+/4+ proteinuria requires treatment for relapse. Prednisolone is given at a dose of 2 mg/kg/day until protein is negative/trace for 3 consecutive days, and then on alternate days at a dose of 1.5 mg/kg for 4 weeks. Treatment for a relapse usually lasts for 5–6 weeks, and there is no evidence that prolonged therapy of a relapse determines the outcome of the illness. If the patient is not in remission despite 2 weeks treatment with daily prednisolone, the treatment is extended for 2 more weeks. Patients showing no remission despite 4 weeks' treatment are labeled as *late steroid resistance*.

The first 2–3 relapses are treated in the manner described above. Once the pattern of relapses is known, therapy is individualized. Patients with infrequent relapses continue to receive treatment for individual relapses as outlined above.

Infrequent Relapses
Patients suffering from three or fewer relapses a year should receive 5–6 weeks treatment for each disease relapse as described above.

Frequent Relapses and Steroid Dependence
Patients with frequent relapses or steroid dependence require prolonged treatment in order to maintain disease remission. Strategies used to maintain remission are described in **Table 2**.

Long-term, Alternate Day Steroids
This is the usually the first strategy in managing patients with frequent relapses. Following treatment of a relapse, the dose of prednisolone is gradually tapered to a small dose given on alternate days to maintain the patient in remission. This strategy is effective in maintaining remission in 40–50% patients. Evidence suggests that changing the frequency of administration of prednisolone from alternate day to daily for 5–7 days during minor infectious illnesses is effective in preventing infection precipitated relapses.

Steroid Sparing Agents
The use of an alternative agent should be considered in patients with: (1) prednisolone threshold (for maintaining remission) higher than 0.5–0.7 mg/kg on alternate days, or (2) features of corticosteroid toxicity. The agents used are listed below:

Levamisole This agent is effective in reducing relapses and steroid requirement in many patients with frequent relapses and steroid dependence. The dose of prednisolone is decreased every 2–4 weeks to 0.25–0.5 mg/kg on alternate days. While therapy with prednisolone may be discontinued in some cases, many patients continue to require a small dose on alternate days. Adverse effects are uncommon. Leukocyte counts are monitored every 2–3 months.

Cyclophosphamide Therapy with cyclophosphamide is effective in ensuring sustained steroid free remission in a significant proportion of patients. The agent is preferred in patients with: (a) significant steroid toxicity, (b) severe relapses with episodes of hypovolemia, life-threatening infections or thrombosis, and (c) poor compliance or difficult follow-up. Children older than 7–8 years, those with frequent relapses and lower steroid threshold do better than those who are younger or have steroid dependence.

In view of its toxicity profile **(Table 2)**, the cumulative dose of cyclophosphamide should not exceed 168 mg/kg, and repeat courses are avoided. Leukocyte counts are monitored every 2 weeks and the medication discontinued if below 4,000/mm^3. Fluid intake is increased and the child is encouraged to void frequently. The dose of prednisolone is 1–1.5 mg/kg on alternate

Table 2 Alternative agents in steroid sensitive nephrotic syndrome

Agent	Dose	Duration	Adverse effects
Long-term alternate day prednisolone	0.3–0.7 mg/kg on alternate days	9–24 months	Cushingoid habitus, short stature, hypertension, cataract, glaucoma
Levamisole	2–2.5 mg/kg on alternate days	1–3 years	Rare: leukopenia, flu-like illness, rash, seizures
Cyclophosphamide*	2–2.5 mg/kg daily	8–12 weeks	Leukopenia, nausea, nail discoloration, alopecia Prolonged therapy: gonadal toxicity, malignancies
Mycophenolate mofetil	600–1,000 mg/m^2/day; 20–25 mg/kg/day	1–3 years	Gastrointestinal discomfort, diarrhea, leukopenia
Cyclosporine A (CyA) or tacrolimus (Tac)*	4–5 mg/kg/day; 0.1–0.2 mg/kg/day (target trough 80–120 ng/mL; 3–7 ng/mL, respectively)	2–3 years	Acute, chronic nephrotoxicity CyA > Tac: hirsuitism, gum hyperplasia, hypertension, high cholesterol Tac > CyA: high sugar and transaminases, diarrhea, headache, seizures
Rituximab*	375 mg/m^2 weekly	2–4 doses	Infusion reactions (rash, fever, chills, anaphylaxis); synovitis, agranulocytosis; acute lung injury

These agents are used in successive order from top to bottom. Agents marked with an asterisk (*) are preferred in patients with significant steroid toxicity (cataracts, severe stunting, obesity) or if disease relapses are associated with life-threatening complications (thrombosis, severe infections).

days during cyclophosphamide therapy; subsequently steroids are tapered and discontinued over 4–6 weeks. Another alkylating agent, *chlorambucil,* though effective has significant additional toxicities and a low margin of safety, and is not recommended.

Mycophenolate mofetil The use of mycophenolate mofetil in large case series of patients with relapsing nephrotic syndrome has been associated with reduced relapse rates and significant steroid sparing. Tapering doses of prednisolone are administered for 6–12 months. Therapy is generally safe and associated with few side effects. Leukocyte counts are monitored every 1–2 months and treatment withheld if below 4,000/mm³.

Cyclosporine and tacrolimus Therapy with either of these agents is indicated in patients with frequent relapses that fail to benefit with levamisole, cyclophosphamide and/or mycophenolate mofetil. Both agents have strong steroid sparing potential, with steroid discontinuation achieved in a majority of patients. However, treatment is associated with significant risk of adverse effects and cautious use under the supervision of an expert is necessary. Therapy with either agent is administered for 2–3 years while targeting trough levels **(Table 2)** and monitoring renal function every 3 months; rise of creatinine more than 25% is of concern. In view of risk of nephrotoxicity, a renal biopsy is done prior to and after 2–3 years of therapy.

Rituximab This monoclonal anti-CD20 antibody has been shown to have efficacy in patients with steroid-dependent nephrotic syndrome. Therapy is recommended in patients with marked steroid dependence not responding satisfactorily to other therapies, or having toxicity to other drugs. Rituximab should be administered under close supervision only at specialized centers.

STEROID-RESISTANT NEPHROTIC SYNDROME

The diagnosis of steroid resistance is made if there is lack of remission despite treatment with prednisolone, at a dose of 2 mg/kg/day (60 mg/m²/day) for 4 weeks **(Box 1)**. The definition is based on the knowledge that 95% patients with steroid sensitive nephrotic syndrome achieve remission within 4 weeks of steroid therapy, and that longer therapies are associated with high incidence of medication-related adverse effects. Care is taken to exclude systemic infections (*e.g.,* peritonitis, cellulitis, respiratory tract infections), which might result in persistent proteinuria. Initial resistance is defined by the lack of remission at the first episode of nephrotic syndrome, and late resistance is considered in patients who are steroid sensitive initially, but show steroid resistance during a subsequent relapse. The management of these patients is difficult, with patients showing variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage.

Evaluation

Baseline assessment of renal function, levels of albumin and cholesterol, and quantification of urinary protein loss (spot urine protein to creatinine ratio in young children; or 24 hours protein excretion) are essential to guide management and evaluation of response to therapy.

Children diagnosed with steroid-resistant nephrotic syndrome should undergo renal biopsy before instituting specific treatment. While patients with minimal change disease show a satisfactory response to therapy, presence of FSGS with tubulointerstitial changes is associated with less satisfactory outcomes. The diagnosis of entities such as MPGN and membranous nephropathy is important, since their management differs from idiopathic minimal change and FSGS. All patients should be evaluated for hepatitis B and C virus infection, particularly if renal histology shows membranous nephropathy or MPGN.

About 10–20% patients with familial and sporadic steroid resistance might carry homozygous or compound heterozygous mutations in genes encoding podocyte proteins, most commonly podocin (*NPHS2*), nephrin (*NPHS1*) and Wilms tumor (*WT1*). These patients are usually unresponsive to immunosuppressive medications, progress rapidly to end stage renal disease, and unlike nongenetic FSGS (which recurs after transplantation in 30%), do not show post-transplantation recur. Patients with syndromic forms have onset of disease in early childhood, e.g., Denys-Drash syndrome (diffuse mesangial sclerosis, Wilms tumor), Frasier syndrome (FSGS, male pseudohermaphroditism, gonadoblastoma) and Pierson syndrome (diffuse mesangial sclerosis, microcoria, neurological abnormalities). Where facilities exist, mutational analysis should be offered to patients with: (1) congenital nephrotic syndrome (onset below 3 months of age), (2) family history of steroid resistance, (3) sporadic initial steroid resistance that does not respond to therapy with cyclophosphamide or calcineurin inhibitors, and (4) girls with steroid-resistant FSGS.

Management

Patients with idiopathic steroid resistance secondary to minimal change disease, FSGS or mesangioproliferative glomerulonephritis are treated similarly. Patients with minimal change disease demonstrate higher rates of remission and better prognosis. *The chief factor predicting renal outcome is the response of proteinuria to therapy rather than the renal histology.* The aim of therapy in patients is thus to induce and maintain remission of proteinuria, while avoiding medication-related adverse effects. Most regimens use a combination of an immunosuppressive agent with prednisolone (given on alternate days) and an angiotensin converting enzyme inhibitor **(Table 3)**.

Calcineurin Inhibitors (Cyclosporine or Tacrolimus)

Treatment with calcineurin inhibitors is considered *first line* for patients with steroid resistance. Cyclosporine and tacrolimus are effective in inducing complete or partial remission in 60–80% patients. Adverse effects are common, as described above, and require close monitoring.

Cyclophosphamide

Oral cyclophosphamide administered alone or with oral steroids, has limited efficacy in inducing remission. Cyclophosphamide has also been used, with modest success, either in the intravenous form or in combination with intravenous steroids. Intravenous cyclophosphamide, when administered monthly for 6 doses along with tapering doses of prednisolone, induces remission in 40–50% patients.

Pulse Corticosteroids with Oral Cyclophosphamide

Pulses of IV methylprednisolone or dexamethasone have been used in combination with oral cyclophosphamide with moderate efficacy. The risk of steroid toxicity is high, with a significant proportion of patients developing systemic infections, hypertension and electrolyte abnormalities.

Other Agents

Rituximab has been reported to be successful in inducing disease remission in 25–30% patients. Its safety and efficacy needs to be established in larger series. Other therapies that have shown promise, in anecdotal reports, include the combination of cyclosporine and mycophenolate mofetil, abatacept and plasmapheresis.

Adjunctive Therapies

Prednisolone Prednisolone is a component of all regimens. It is administered on alternate days at 1 mg/kg day for 1–3 months,

Table 3 Agents for management of steroid resistant nephrotic syndrome

Agent	Dose	Duration	Efficacy	Adverse effects
Calcineurin inhibitors				
Cyclosporine (CsA)	4–5 mg/kg/day	12–36 months	50–80%	Common: Acute and chronic nephrotoxicity; hirsuitism and gum hyperplasia (CsA > Tac); hypertension; high cholesterol (CsA > Tac); hyperglycemia (Tac); elevated transaminases; neurotoxicity with headache and seizures (Tac > CsA)
Tacrolimus (Tac)	0.1–0.2 mg/kg/day	12–36 months	70–85%	
Cyclophosphamide				
Intravenous	500–750 mg/m^2	6 pulses	40–50%	Leukopenia; alopecia; nausea and vomiting (IV > oral); gonadal toxicity; hemorrhagic cystitis (IV > oral)
Oral	2–2.5 mg/kg/day	12 weeks	20–25%	
High dose corticosteroids with cyclophosphamide				
Methylprednisolone or	20–30 mg/kg IV		30–50%	Hypertension, hypokalemia, hyperglycemia, steroid psychosis, systemic infections
Dexamethasone	4–5 mg/kg/day IV			
	Pulses on alternate days × 6; once weekly × 8, fortnightly × 4, monthly × 8, bimonthly × 4 (abbreviated protocols also used)			Side effects of cyclophosphamide and prolonged steroid therapy
Prednisolone	Tapering doses × 18 months* PO			
Cyclophosphamide	2–2.5 mg/kg/day × 12 weeks** PO			

*Prednisolone 1.5 mg/kg on alternate days × 4 weeks; 1.25 mg/kg × 4 weeks; 1 mg/kg × 4 months; 0.5–0.75 mg/kg × 12–18 months.
**Cyclophosphamide is administered during 3–12 weeks.

following which the dose may be tapered. Prednisolone may be discontinued if the child is in sustained complete remission for 6–12 months.

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers Therapy with angiotensin converting enzyme (ACE) inhibitors (e.g., enalapril 0.3–0.6 mg/kg/day, ramipril 6 mg/m^2/day) is associated with decrease in proteinuria and control of hypertension. Adverse effects include dry cough, hyperkalemia and decline in renal function. The dose of ACE inhibitor is decreased or therapy discontinued if hyperkalemia develops or eGFR falls less than 30 mL/minute/1.73 m^2. Angiotensin receptor blockers (e.g., losartan, valsartan) may be used in case of persistent dry cough with ACE inhibitors, or as add-on therapy for enhanced antiproteinuric effect. There are limited studies on the efficacy of this combination and it may be associated with significant toxicity.

Monitoring Response to Therapy
Patients should be monitored every month until response is demonstrated, and then every 2–3 months. *Complete remission* is defined as presence of trace or negative proteinuria (by dipstick) or spot urine protein to creatinine ratio (Up/Uc) less than 0.2 mg/mg. Patients are considered to be in *partial remission* if they show 1-2+ proteinuria (or Up/Uc between 0.2-2), blood albumin more than 2.5 g/dL and no edema. *Nonresponse* is defined as 3-4+ proteinuria (Up/Uc > 2), albumin less than 2.5 g/dL or edema. The aim of treatment is achievement of complete remission, but occurrence of partial remission is also satisfactory. Patients who respond to treatment do so within 3–6 months; those that fail therapy with one regimen may respond to different agents.

Monitoring for Adverse Effects of Drugs
Most agents used in the therapy of steroid resistance require monitoring for adverse effects. Monitoring for drug levels is recommended when using either cyclosporine or tacrolimus, because individual variations in bioavailability may result in occurrence of either subtherapeutic or toxic levels. A 12 hours trough level should be estimated about 2 weeks after introduction

of therapy, after any dose change, and if suspecting drug toxicity or poor compliance. Trough levels in the range of 80–120 ng/mL for cyclosporine and 4–7 ng/mL for tacrolimus are acceptable. Examination of renal histology is advised in patients receiving prolonged therapy (2–3 years) with calcineurin inhibitors. Histological features of nephrotoxicity include nodular hyalinosis or striped interstitial fibrosis and tubular atrophy. Prolonged duration of therapy (exceeding 2–3 year) and persistent heavy proteinuria (beyond 30 days) are risk factors for nephrotoxicity.

Duration of Therapy
Consensus is lacking on the optimal duration of treatment with calcineurin inhibitors. Therapy is continued for 2–3 years in patients that show complete or partial remission, followed by the options: (1) taper dose of the medication to the lowest effective dose, and continue for another 1–2 year; (2) exclude medication-related nephrotoxicity on renal histology and then continue therapy; (3) switch treatment to a less toxic agent, e.g., mycophenolate mofetil or rituximab.

Recurrence of FSGS after Renal Transplantation
Focal segmental glomerulosclerosis recurs in 30–50% of children following renal transplantation, leading to graft loss in half of these patients. Risk factors for recurrence are: (1) nongenetic forms of FSGS, (2) progression to end-stage renal disease within 2 years of onset of disease, (3) mesangial proliferation on original biopsies and (4) nephrectomy of native kidneys prior to transplant. Pretransplant plasmapheresis is an important preventive strategy. While there is no consensus on optimal therapy of patients with recurrent FSGS, options include: (1) intensive plasmapheresis; (2) high dose cyclosporine or tacrolimus; (3) rituximab; and (4) oral cyclophosphamide instead of mycophenolate mofetil.

CONGENITAL NEPHROTIC SYNDROME
Congenital nephrotic syndrome is defined as the presence of nephrotic syndrome within the first 3 months of life. While the Finnish type and other inherited defects are considered

the most common forms, its etiology is diverse, and includes: (1) Inherited mutations in genes encoding nephrin (*NPHS1*) (Finnish type); podocin (*NPHS2*) gene, phospholipase C epsilon 1 (*PLCE1* or *NPHS3*); Wilms tumor suppressor 1 (*WT1*) (Denys Drash syndrome; isolated nephrotic syndrome); laminin β2 (*LAMB2*) (Pierson syndrome; isolated nephrotic syndrome); laminin β3 (*LAMB3*) (Herlitz junctional epidermolysis bullosa); Lim transcription factor 1β (*LMXB1*) (nail-patella syndrome); (2) Galloway-Mowat syndrome (congenital nephrotic syndrome with microcephaly, developmental delay, hiatal hernia, diffuse mesangial sclerosis); (3) mitochondrial disorders; (4) primary FSGS; (5) congenital infections: syphilis, toxoplasma, malaria, cytomegalovirus, rubella, hepatitis B, human immunodeficiency virus; (6) maternal systemic lupus; and (7) maternal therapy with steroids and chlorpheniramine.

Clinical Features
Patients with congenital nephrotic syndrome present with edema at or soon after birth. Patients with the classical Finnish type of nephrotic syndrome are born premature, with large placentae, and wide cranial sutures and fontanelles. Failure to thrive, delayed development, hypothyroidism and repeated infections are noted. Common complications include hypotension (hypovolemia), spontaneous vascular thrombosis, hypertension and anemia (disease progression). Presence of associated abnormalities may suggest the diagnosis in infants with Galloway-Mowat syndrome (severe psychomotor retardation, hypotonia, and seizures), Pierson syndrome (microcoria) and Denys-Drash syndrome (ambiguous genitalia).

Evaluation
Investigations show nephrotic range proteinuria, low serum albumin (usually < 1 g/dL), elevated thyroid stimulating hormone and dyslipidemia. Renal function is normal but deranged in older infants and beyond infancy. Appropriate serology helps detect rare cases associated with congenital infections. Sequencing of *NPHS1* enables diagnosis of the Finnish nephrotic syndrome, also reported in individuals of non-Finnish ancestry. Mutations in other genes (*NPHS2*, *WT1* and *LAMB2*) might be important in patients of Asian ethnicity.

Histology
Renal biopsy shows microcysts in the cortex, representing dilatation of proximal convoluted tubules. Mesangial proliferation, thickened Bowman capsule and increase in mesangial matrix are common. Electron microscopy reveals effacement of foot processes, thin glomerular basement membrane, mild endothelial swelling and disappearance of the slit diaphragms. Histological changes may be absent if the renal biopsy is obtained early in the disease. The histology is evaluated in context of results of genetic testing; FSGS is common in patients with *NPHS2* mutations, while patients with mutations in *WT1, LAMB2* and *PLCE1* genes show diffuse mesangial sclerosis.

Management
Establishing the diagnosis is important for prognosis, therapy and genetic counseling. Management is difficult and outcomes are unsatisfactory. Immunosuppression has no role in managing infants with congenital nephrotic syndrome. Patients with congenital syphilis or toxoplasmosis may occasionally respond to appropriate antimicrobials. Control of edema requires the use of loop and thiazide diuretics, and frequent albumin infusions (20%, 1–4 g/kg/day, as required). Nutritional support is important to maintain well-being, and the diet should provide 120–130 Cal/kg/day and 3–4 g/kg/day proteins. Supplements of vitamins A, D, E and water-soluble vitamins, calcium and magnesium are provided. Nasogastric feeds may be necessary to ensure adequate intakes. A small dose of thyroxin (6.25–12.5 µg/day) is given, adjusted to TSH levels. Interventions that have been used to reduce proteinuria include: (1) ACE inhibitors (captopril 3–4 mg/kg/day or enalapril 0.2–0.5 mg/kg/day); (2) indomethacin (1–2 mg/kg/day); (3) unilateral or bilateral nephrectomy with institution of continuous peritoneal dialysis. Transplantation is offered once the body weight exceeds 9 kg.

Prognosis
Most affected children succumb to illness during infancy, either to infections or complications of the persisting nephrotic state. Children surviving past infancy show progressive kidney disease and require renal replacement therapy. Recurrent disease in the allograft is rare.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS
Membranoproliferative glomerulonephritis (MPGN) refers to a pattern of glomerular injury seen in a variety of diseases having in common, complement activation. The disease causes nephrotic syndrome usually in older children; other presentations include microscopic or gross hematuria with proteinuria, and rarely, rapidly progressive glomerulonephritis.

Classification
Light microscopy is characterized by diffuse mesangial cell proliferation and thickening of capillary walls due to subendothelial extension of the mesangium **(Fig. 1C)**. Based on findings on immunofluorescence and electron microscopy, two subtypes are recognized. Immune complex MPGN (previously type 1 MPGN) characterized by subendothelial immune complex deposits is secondary to activation of the classic complement pathway. Causes of immune complex MPGN include infections with hepatitis B or C viruses, lupus erythematosus, lymphoma, lipodystrophy and cryoglobulinemia. Evidence of activation of the classic complement pathway (normal or low serum C3, low C4) is present. C3 nephropathy (previously type II MPGN) is characterized by predominant presence of C3 deposits without significant immune complexes on immunofluorescence. Most patients have evidence of alternative pathway activation (markedly low serum C3, normal C4). A proportion of patients with C3 nephropathy show dense ribbon-shaped intramembranous deposits of C, in association with C3 nephritic factor, a circulating immunoglobulin that stabilizes C3 convertase resulting in persistent activation of the alternative complement pathway; others show factor H deficiency or dysfunction.

Management
The disorder is slowly progressive, with high-risk for renal failure particularly in C3 nephropathy. Factors indicating poor outcome are persistent heavy proteinuria, raised serum creatinine at the onset, presence of cellular crescents and tubulointerstitial disease. Long-term administration of alternate day prednisolone (1–1.5 mg/kg) combined with an angiotensin-converting enzyme inhibitor with or without mycophenolate mofetil may be useful. The role of eculizumab, a monoclonal antibody against C5, in interrupting complement activation is being investigated. Patients should be screened for hepatitis B and C infection before initiating immunosuppressive therapy. The majority of patients with dense deposit disease show recurrent illness in the transplanted kidney.

MEMBRANOUS NEPHROPATHY
Membranous nephropathy is an uncommon cause of nephrotic syndrome in childhood. Most cases are idiopathic, but the

disease may be secondary to lupus, infection with hepatitis B, Epstein-Barr virus, schistosomiasis and malaria, or exposure to medications (gold, penicillamine, nonsteroidal anti-inflammatory drugs). A majority of adult patients with idiopathic membranous glomerulonephritis (MGN) show autoantibodies to M type isoform of phospholipase A2 receptor; similar data in children is lacking. MGN is characterized by a diffuse thickening of the capillary basement membrane with subepithelial deposits and little or no cellular proliferation **(Fig. 1D)**. While in early stages light microscopy may be normal, IgG deposits are seen on immunofluorescence and in the subepithelial region on electron microscopy.

Management

Therapy with angiotensin converting enzyme inhibitors is effective in reducing proteinuria, and is recommended in all cases. Initial immunosuppressive regimen for primary MGN includes therapy with prednisolone and cyclophosphamide, failing which a calcineurin inhibitor (cyclosporine, tacrolimus) is recommended. A variable proportion of patients failing the above therapies respond to 2–4 doses of IV rituximab. Patients with hepatitis B-associated MGN may be treated with interferon-alpha and/or other antiviral agents.

SUPPORTIVE CARE AND MANAGEMENT OF COMPLICATIONS

Patients with relapsing steroid sensitive nephrotic syndrome and those with steroid-resistant disease require attention for complications resulting from disease or its therapy. Patients should be maintained in remission, as far as possible. Relapses should be promptly treated so that the child does not develop more than minimal edema.

Edema

Presence of significant edema or anasarca is associated with discomfort and an increased risk of infections. Since daily administration of corticosteroids results in diuresis within 2–4 days, most patients do not require specific therapy for edema, particularly if urine protein is monitored at home. Those with significant edema and weight gain require treatment with diuretics.

Management

Edema is usually controlled with salt restriction and oral furosemide for a few days. **Flow chart 1** outlines the stepwise treatment of edema in children with nephrotic syndrome. Edema that does not respond to maximal doses of oral furosemide requires co-administration of thiazides (e.g., hydrochlorothiazide, metolazone). If furosemide is used for prolonged duration (> 7 days) or in high doses (3–6 mg/kg/day), use of spironolactone (2–4 mg/kg/day) prevents hypokalemia. Parents are instructed to discontinue diuretics if symptoms of hypovolemia (abdominal pain, dizziness) appear, or the child has diarrhea, vomiting or poor oral intake.

Patients with refractory edema should be hospitalized and administered IV furosemide either as boluses (1–3 mg/kg/dose IV over 15–20 minutes) or as continuous infusions (0.1–1 mg/kg/hour), under careful monitoring. Infusions of albumin (20% albumin, 0.5–1 g/kg, over 2–4 hours), with an IV bolus of furosemide, administered at the end of the infusion, are useful in patients with severe hypoalbuminemia. However, the effect is transient, requiring repeat administration in patients with severe edema. Care must be taken to avoid IV albumin in patients with oliguria, who may show worsening hypertension or congestive cardiac failure. Albumin administration should be avoided in individuals with oligoanuria and respiratory distress. Patients with refractory severe ascites and respiratory distress may require paracentesis, which should be done carefully under aseptic precautions. Hospitalized patients must be monitored carefully with daily record of weight and urine

Flow chart 1 Management of edema in patients with nephrotic syndrome
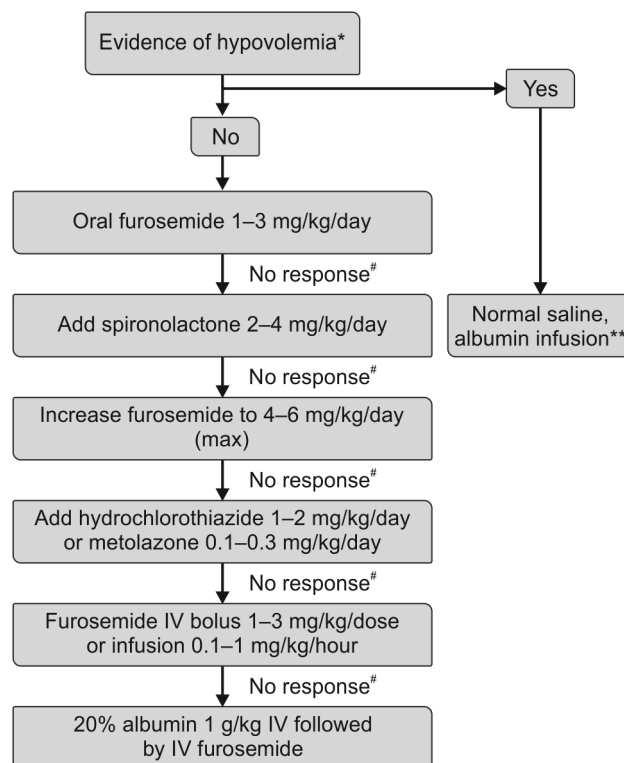
*Hypovolemia is suggested by the presence of tachycardia, feeble pulses, cold extremities or hypotension. Additional features include elevated hematocrit, disproportionately high blood urea, low fractional excretion of sodium (< 0.5%) and urinary $K^+/(K^+ + Na^+)$ more than 0.6. **Management of hypovolemia consists of rapid infusion of normal saline at a dose of 15–20 mL/kg over 20–30 minutes, repeated as required. Infusion of 5% albumin (10–15 mL/kg) or 20% albumin (0.5–1 g/kg) is useful in subjects who do not respond to two boluses of saline. #No weight loss or diuresis in 48 hours; or weight gain.

output, frequent monitoring of vital signs and daily estimation of electrolytes (hypokalemia, hyponatremia and metabolic alkalosis).

Hypovolemia

Hypovolemia may occur during severe disease relapse or following administration of diuretics, particularly in children with poor intake, diarrhea and vomiting. Features include abdominal pain, lethargy, dizziness and leg cramps, tachycardia, hypotension, delayed capillary refill, low volume pulses and cool clammy peripheries. An elevated ratio of blood urea to creatinine and rising hematocrit suggest the presence of hypovolemia. The level of urine sodium and its fractional excretion are reduced to less than 20 mEq/L and 0.2–0.4% respectively. A high urinary potassium index, urine $K^+/(urine K^+ + Na^+)$ exceeding 0.6 suggests presence of hypovolemia.

Therapy with diuretics should be discontinued. When signs of hypovolemia are absent, an increase in oral fluid intake alone may suffice. With features of hypovolemia, patients require admission and rapid infusion of normal saline (10–20 mL/kg) over 20–30 minutes. Patients who do not respond to two boluses of saline should receive infusion of 5% albumin (10–15 mL/kg) or 20% albumin (0.5–1 g/kg).

Infections

Common infections include peritonitis and cellulitis, which should be treated using appropriate antibiotics. Complications of varicella

may be life-threatening in patients with nephrotic syndrome receiving corticosteroids or other immunosuppressive drugs. All patients with varicella must receive oral acyclovir for 7 days; severe illness requires admission and administration of IV acyclovir. Administration of varicella zoster immunoglobulin (single dose within 96 hours of exposure), or intravenous immunoglobulin (400 mg/kg, single dose) prevents or lessens the severity of the disease in susceptible individuals.

Hypertension

Hypertension may be noted at the onset of disease or develop secondarily as a result of high dose steroid therapy. Persistent elevation in blood pressure, refractory to control of edema and decline of corticosteroid dose, merits treatment. An angiotensin converting enzyme inhibitor, enalapril (0.3–0.6 mg/kg/day in two divided doses) or ramipril is the medication of choice. The dose is increased to permissible limits in patients with persistent hypertension, while monitoring renal function and levels of potassium. Some patients require additional therapy with calcium channel blockers (e.g., amlodipine) or adrenergic blockers. The target blood pressure is between the 75th percentile and 90th percentile for age, gender and height.

Dyslipidemia

Patients with steroid-resistant nephrotic syndrome with persistent proteinuria have continued dyslipidemia that is undesirable, and requires treatment. Therapy with HMG-CoA reductase inhibitors (atorvastatin 10–20 mg daily in children greater than 5 years) is recommended in presence of biochemical abnormalities that persist for 3–6 months: total cholesterol more than 200 mg/dL or low-density lipoprotein cholesterol more than 130 mg/dL.

Thrombosis

Children with nephrotic syndrome are predisposed to venous thromboembolism during relapses, due to multiple reasons including loss of antithrombin III, low intravascular volume (aggressive diuretic use, diarrheal dehydration), immobilization, indwelling catheters and puncture of deep vessels. Thrombosis should be suspected in patients with hematuria or flank pain (renal vein thrombosis); venous congestion, pain, reduced mobility of limbs (deep vein thrombosis); or seizures, vomiting, altered sensorium and neurological deficits (sagittal sinus or cortical venous thrombosis). Diagnosis requires confirmation with ultrasonography, Doppler studies and cranial MRI if required. Therapy includes use of heparin or low-molecular-weight heparin initially, followed by oral anticoagulants for 4–6 months.

Vaccination

Administration of live vaccines (oral polio, varicella) should be deferred until the child is off immunosuppressive medications for at least 4 weeks. If essential, these vaccines may be given to patients receiving alternate day prednisolone at a dose less than 0.5 mg/kg. The administration of pneumococcal vaccine is desirable. Children below 2 years of age should receive the pneumococcal conjugated vaccine, 0.5 mL intramuscularly, in the schedule advised by the Indian Academy of Pediatrics. Above 2 years, one dose of the polysaccharide vaccine (PPV23) is administered, following one dose of the conjugate vaccine; the gap between the injections should be at least 2 months. Children who continue to have relapses of nephrotic syndrome may receive one repeat dose of PPV23, 5 year after the primary vaccination.

Two doses of the varicella vaccine are given 4 weeks apart while the child is in remission and off immunosuppressive medications. Injectable polio vaccine may be given to children with nephrotic syndrome and their siblings. If the child has received primary immunization with oral polio vaccine (6, 10 and 14 weeks), two doses of parenteral vaccine are given at 2 months interval followed by a third dose 6 months after the first dose, and a booster at 5 years.

Nutrition

During remission, children should eat a balanced, nutritious diet without restrictions. If relapses are associated with edema, salt restriction is advised, by curbing the intake of snacks and foods with high salt content. Undue restriction that makes food unpalatable is not required. Patients with persistent or recurrent proteinuria should increase their intake of proteins to 2–2.5 g/kg/day. Increase in physical activity can help achieve desirable body weight in those with Cushingoid features or obesity. Patients on prolonged therapy with prednisolone (> 3 months) should receive supplements of calcium carbonate (250–500 mg) and vitamin D (125–250 IU).

Stress Dose of Steroids

Patients who have received steroids at high doses for more than 2 weeks in the past year are at risk of suppression of the hypothalamo-pituitary-adrenal axis. These children require steroid supplements during surgery, anesthesia or serious infections. Corticosteroids are supplemented, as parenteral hydrocortisone at a dose of 2–4 mg/kg/day, followed by oral prednisolone at 0.3–0.6 mg/kg/day. This is given for the duration of stress and then tapered rapidly.

The long-term management of nephrotic syndrome requires frequent interactions with patients' families to ensure their cooperation in disease management. Parents are explained the natural history of the disease and its outcome, and the expected adverse effects of repeated courses of high dose steroid therapy and other medications. While steroid responsiveness remains the most important prognostic feature, patients with both steroid sensitive and steroid-resistant disease require close monitoring of disease course and timely management of disease and therapy-related complications in order to enable satisfactory long-term outcomes.

IN A NUTSHELL

1. Nephrotic syndrome is the most common chronic kidney disease of childhood. The majority (85–90%) is steroid responsive; minimal change nephrotic syndrome accounts for more than 75% cases.
2. The precise cause of idiopathic nephrotic syndrome is unclear, but has been attributed to aberrant immune system with Th2 predominance and/or downregulation of T regulatory axis. Others suggest a primary defect in the podocyte slit diaphragm or actin cytoskeleton; mutations in a number of genes encoding podocyte proteins have been described. The role of circulating mediators that affect glomerular permeability is being examined.
3. Steroid responsiveness is the chief prognostic factor that determines long-term outcomes.
4. In patients with steroid sensitive nephrotic syndrome, prudent use of corticosteroids and steroid sparing agents is recommended to avoid side effects of therapy and complications associated with the illness.
5. Calcineurin inhibitors are the drugs of choice for patients with steroid-resistant nephrotic syndrome. Patients with steroid resistance who fail to respond to the above therapy are at risk for progressive renal disease.
6. Common complications of nephrotic syndrome include life-threatening infections (peritonitis, cellulitis), thrombotic events, hypovolemia, progressive renal failure and side effects of immunosuppressive agents.

MORE ON THIS TOPIC

Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome—current and future therapies. Nat Rev Nephrol. 2012;8:445-58.

Lombel RM, Gipson DS, Hodson EM; Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013;28:415-26.

Lombel RM, Hodson EM, Gipson DS; Kidney Disease: Improving Global Outcomes. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatr Nephrol. 2013;28:409-14.

Oh J, Kemper MJ. Minimal change (steroid sensitive) nephrotic syndrome in children: new aspects on pathogenesis and treatment. Minerva Pediatr. 2012;64:197-204.

Ponticelli C, Graziani G. Current and emerging treatments for idiopathic focal and segmental glomerulosclerosis in adults. Expert Rev Clin Immunol. 2013;9:251-61.

Pravitsitthikul N, Willis NS, Hodson EM, Craig JC. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev. 2013;10:CD002290.

Rood IM, Deegens JK, Wetzels JF. Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. Nephrol Dial Transplant. 2012;27:882-90.

Saleem MA. New developments in steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2013;28:699-709.

Segarra-Medrano A, Carnicer-Cáceres C, Arbós-Via MA, et al. Biological markers of nephrotic syndrome: a few steps forward in the long way. Nefrologia. 2012;32:558-72.

Sinha A, Bagga A. Nephrotic syndrome. Indian J Pediatr. 2012;79:1045-55.

Chapter 41.11
Acute Kidney Injury
Anil Vasudevan

Acute kidney injury (AKI), formerly known as acute renal failure is characterized by an abrupt (48 hours to 7 days) and sustained decline in glomerular filtration rate (GFR) and an inability of kidneys to appropriately regulate fluid, electrolytes and acid-base homeostasis. The spectrum of injury ranges from mild to advanced, sometimes requiring renal replacement therapy (RRT). AKI is associated with significant mortality and morbidity, especially in critically ill children. Although the precise incidence in children is not known, data indicate that its incidence is increasing. The etiology of AKI has changed from primary renal disease to multifactorial causes, particularly in hospitalized children.

DEFINITION

The definition of AKI is based on level of serum creatinine and urine output. The current definition and staging of patients with AKI is summarized in **Table 1**. While these definitions have been validated in adults, there is limited data in this regard for children. Although, useful for stratifying children based on severity of illness, there are limitations in the classification. Serum creatinine rises only after 25–50% of kidney function is lost. Besides, creatinine cannot be used to assess kidney function in patients receiving dialysis or in the first few days of life (when they reflect maternal creatinine). Nonoliguric AKI is common in neonates, and hence the urine output criteria might not hold in case of newborns.

EPIDEMIOLOGY

The incidence of AKI varies in different regions of the world; estimates range from 20 cases per year per 100,000 population in neonates to as low as two cases per year per 100,000 population in older children. The coexistence of AKI with critical illness occurs at a rate of 10% and has 50% mortality in children requiring dialysis. A study from a tertiary care center in north India, reported incidence densities of 45.1 and 11.7 AKI cases/1,000 patient days in critically ill and noncritically ill children respectively. The incidence of AKI in critically ill neonates is estimated to be between 8% and 24% and that mortality rates are between 10% and 61%. It is recognized that AKI characteristics and etiology in developing countries differs from that of the developed world is many important ways. AKI is the disease of the young and children in whom volume responsive *prenal* mechanisms are common. *Community acquired* AKI

Table 1 Criteria for diagnosis and staging of acute kidney injury

Stage	Serum creatinine	Urine output
I	Increase ≥ 0.3 mg/dL in < 48 hours, or 1.5–1.9 times increase over 7 days	< 0.5 mL/kg/hour for 6–12 hours
II	Increase 2.0–2.9 times	< 0.5 mL/kg/hour for ≥ 12 hours
III	Increase ≥ 3 times, or > 4.0 mg/dL, or initiation of renal replacement therapy, or if < 18-year-old: eGFR < 35 mL/min/1.73 m^2	< 0.3 mL/kg/hour for ≥ 24 hours, or anuria for ≤ 12 hours

eGFR estimated glomerular filtration calculated using Schwartz formula:
$$\frac{0.43 \times \text{height (cm)}}{\text{Serum creatinine (mg/dL)}}$$

forms a significant proportion of cases, compared to the developed world where *hospital acquired AKI* dominates.

ETIOLOGY, RISK FACTORS AND PATHOPHYSIOLOGY

The underlying causes of AKI are divided into prerenal azotemia, renal injury and postrenal obstruction. In most cases, the true etiology is likely multifactorial, related to a combination of several factors (e.g., hypotension, use of nephrotoxic agents and sepsis). **Table 2** lists common causes of AKI in children. Common causes of AKI in our country are volume loss leading to ischemic renal injury, infections and hemolytic uremic syndrome. In developed countries, most AKI is related to sepsis, use of nephrotoxic agents and renal ischemia (postoperative, bone marrow transplant). AKI in the critical care setting is caused by secondary renal injury rather than primary disease, characteristically acute tubular necrosis. Young age, presence of comorbidities (chronic kidney disease, cardiac disease, liver failure), use of nephrotoxic agents [nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, radiocontrast agents], children receiving stem cell transplants and those undergoing cardiopulmonary bypass are risk factors for AKI. Newborns are particularly at risk as they are susceptible to hypoperfusion, low GFR and might be exposed to nephrotoxic medications and frequent infections. Neonates with hypoxic encephalopathy and those undergoing cardiopulmonary bypass are at high-risk.

Prerenal Acute Kidney Injury

Prerenal azotemia is characterized by diminished effective circulating arterial volume, which leads to inadequate renal perfusion and decreased GFR. Hypovolemia resulting in low renal blood flow activates the autoregulatory mechanisms so as to preserve GFR. The compensatory mechanisms that are triggered include increasing renal sympathetic tone, activation of the renin-angiotensin-aldosterone system, and increased activation of hormones such as vasopressin and endothelin resulting in afferent arteriolar dilatation and efferent arteriolar constriction to maintain the glomerular pressure gradient. These mechanisms enhance proximal tubular sodium and water reabsorption and urea in those with intact tubular function leading to decreased water and sodium losses which help in maintaining systemic volume and blood pressure. If volume is restored, the renal function abnormalities are reversible.

Acute Tubular Necrosis

Acute tubular necrosis (ATN), characterized by renal tubular injury may occur due to ischemia/hypoperfusion or due to injury from drugs or toxins **(Table 2)**. Ischemic ATN is a continuum of physiologic responses that is observed in prerenal azotemia. It is characterized by parenchymal damage, chiefly affecting the medullary S3 segment of the proximal tubule and medullary portion of the thick ascending limb of Henle. If ischemia/hypoperfusion is severe and prolonged, ATN can progress to renal infarction and corticomedullary necrosis with irreversible renal damage. Pathophysiologically, the course of ischemic AKI may be subdivided into four phases: initiation (decrease in perfusion and depletion of ATP), extension (ischemia reperfusion injuries aggravating tubular injury), maintenance (tubular injury persists due to persistence of inflammation) and recovery (repair and regeneration of tubular cells). The initiation phase includes the primary insult resulting in a drop in GFR and the tubular dysfunction. The duration of the maintenance phase depends on the severity and duration of the initial insult. These phases are characterized by oligoanuria. The recovery phase is characterized

Table 2 Etiology of acute kidney injury

Prerenal	Renal	Postrenal
Decreased true intravascular volume	*Glomerular*	*Obstructive uropathy*
Severe diarrhea, vomiting	Postinfectious glomerulonephritis	Ureteropelvic
Burns	Crescentic glomerulonephritis	junction obstruction
Hemorrhage, trauma	*Vascular lesions*	Bilateral ureteral
Sepsis	Hemolytic uremic syndrome	obstruction
	Cortical necrosis	Urethral obstruction
Decreased effective intravascular volume	Renal vein or artery thrombosis	Posterior urethral
Anaphylaxis		valves
Septic shock	*Acute tubular necrosis*	
Dengue hemorrhagic fever	*Endogenous toxins:* Intravascular hemolysis, rhabdomyolysis,	*Nephrolithiasis*
Cardiac failure	tumor lysis syndrome	*Neurogenic bladder*
	Exogenous toxins: Ethylene glycol, methanol	
Medications	*Drugs:* Nephrotoxic agents	
Indomethacin	Hypoxic ischemic insult	
Angiotensin converting enzyme inhibitors		
Angiotensin receptor blockers	*Acute tubulointerstitial nephritis*	

by restoration of GFR and tubular functions and manifests with polyuria initially, after which the urine output returns to normal. Complete recovery may take months when the initial insult is severe.

Infection-associated Acute Kidney Injury

Sepsis is a leading cause of AKI in children. Based on various experimental studies in animal models, understanding of sepsis-associated AKI pathophysiology is shifting from renal vasoconstriction, ischemia, and acute tubular necrosis to inflammatory mediator effects on renal vascular endothelium and microcirculatory dysfunction characterized by unbalanced homeostasis between nitric oxide, reactive oxygen species and renal oxygenation.

Malaria may present either as AKI alone or as part of a multiorgan dysfunction. Volume depletion, gastrointestinal bleeding, sepsis, nephrotoxic drugs and hyperbilirubinemia act as predisposing factors. The pathogenesis of AKI is not clearly known. Different hypotheses proposed include hypovolemia, cytokine and nitric oxide-mediated arterial vasodilatation, resistance to vasoactive hormones, cytopathic hypoxia leading to decreased ATP synthesis and mechanical obstruction by infected erythrocytes (cytoadherence). Renal histology consistently shows ATN and interstitial nephritis and glomerulonephritis (GN) may also be seen.

The incidence of AKI in severe leptospirosis varies from 40% to 60%. Clinical manifestations are biphasic, with an initial septicemic phase lasting 3–7 days followed by an immune phase, during which nephropathy occurs. The pathogenetic mechanisms include bacterial invasion, inflammatory processes, hemodynamic alterations and toxicity of bacterial products. AKI in leptospirosis is primarily nonoliguric, and hypokalemia occurs frequently due to kaliuresis; histology shows interstitial nephritis. Leptospirae may be detected in the urine between 1 week and 4 weeks of infection, using dark-field illumination.

Snakebite Envenomation

Snakebites are serious in children because of the relatively large volume of venom injected. Snakes belonging to the families Elapidae, Viperidae, Colubridae and Hydrophiidae cause AKI. Clinical presentations include proteinuria, hematuria, pigmenturia, rhabdomyolysis and myoglobinuria. Kidney injury occurs within a few hours to as late as 96 hours after the bite and is oligoanuric in 94% patients. ATN, with varying degrees of interstitial edema and inflammatory cell infiltration, is the most common histology. Direct nephrotoxicity, hypovolemia, hemolysis, myoglobinuria and disseminated intravascular coagulation are the usual pathogenic mechanisms.

Tumor Lysis Syndrome

Tumor lysis syndrome is seen in patients undergoing first cycle of chemotherapy when rapid tumor destruction occurs, such as in acute myeloid leukemia and lymphomas. Biochemical abnormalities include hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcemia. The precipitation of uric acid crystals in the tubules causes occlusion and decreased filtration.

EVALUATION AND DIAGNOSIS

Clinical features range from asymptomatic with mild to moderate elevation in serum creatinine to anuric renal failure **(Box 1)**. Combining the information from detailed history and physical examination and laboratory investigations can help in identifying the probable casue of AKI. A key part of the evaluation is to identify reversible causes (obstruction, drug-induced AKI).

History and Examination

Edema, hematuria and hypertension suggest a glomerular cause of AKI. History of pyoderma or acute pharyngitis preceding the onset of hematuria, edema and oliguria by few weeks suggests a postinfectious GN. A critically ill child with fever, jaundice, and pallor and hepatosplenomegaly may have AKI secondary to malaria or leptospirosis. Rash or arthritis may suggest vasculitis. A child with history of dysentery and who subsequently develops pallor, petechiae and oliguria is likely to be hemolytic uremic syndrome. A history of interrupted or poor urinary stream with a palpable bladder suggests obstructive uropathy.

A detailed fluid balance history in addition to a history of diarrhea, vomiting, blood loss helps determine the extent to which renal hypoperfusion may be contributing to AKI. Urine

BOX 1 Clinical features of acute kidney injury

- *Decrease or no urine output:* Oliguria < 1 mL/kg/hour; anuria < 0.5 mL/kg/hour
- *Fluid overload:* Edema, tachypnea, abdominal pain, respiratory distress
- *Hypertension:* Headache, vomiting, blurring of vision, seizures
- *Uremia, dyselectrolytemia:* Nausea, vomiting, altered sensorium, encephalopathy, seizures.

output estimation, from history or by quantification, identifies patients with oliguric, anuric or normal urine output and provides clue to the underlying cause. Nonoliguric AKI is seen with toxin or medication-mediated ATN. Anuria is seen in children with urinary tract obstruction, renal cortical necrosis [snake bite, disseminated intravascular coagulation, hemolytic uremic syndrome (HUS)], bilateral renal vein thrombosis and severe dehydration. Information on urine output also help evaluate whether a positive fluid balance is occurring, which suggests that prerenal injury has progressed to cause intrinsic renal injury. Detailed medication history will elucidate its role in mediating AKI (NSAIDs, aminoglycosides, chemotherapeutic agents, angiotensin converting enzyme inhibitors, or radiocontrast agents).

Investigations

Laboratory tests are useful for assessing the etiology and complications of AKI, and management of the disease **(Box 2)**. Urinalysis should be obtained in all children with AKI as it is an informative and noninvasive diagnostic tool. In prerenal AKI, the urine is *bland* with a high specific gravity reflecting appropriate renal retention of water in the setting of renal hypoperfusion. With intrinsic injury, the urine may show mild hematuria and/or proteinuria with a specific gravity 1.015 or less with presence of granular or muddy brown casts and renal tubular epithelial cells. With glomerular injury, the amount of hematuria and proteinuria is moderate to severe. The presence of white blood cells (WBC) or WBC casts suggests pyelonephritis or acute interstitial nephritis. Presence of uric acid crystals or oxalate crystals suggests uric acid nephropathy and ethylene glycol toxicity respectively. While urinary indices may be used to differentiate prerenal from intrinsic renal failure, these indices are not helpful in children who have received diuretics and those with chronic kidney disease or tubular disorders **(Table 3)**.

Imaging

Renal ultrasonography should be performed in children with AKI to rule out obstruction of the urinary collecting system. In intrinsic AKI, the imaging shows increased echogenicity and loss of corticomedullary differentiation of the kidneys. Noncontrast computed tomography may be indicated for evaluation of obstructive AKI (stones, tumor).

Renal Biopsy

Renal biopsy has proven useful in diagnosis and prognostication of select cases (e.g., rapidly progressive GN, hemolytic uremic syndrome, drug-induced AKI) and in children in whom etiology of AKI is not identified particularly in context of systemic disease.

BOX 2 Laboratory investigations in acute kidney injury

Routine
- Urinalysis
- Complete blood counts
- Blood urea, creatinine, electrolytes, calcium, phosphate
- Blood pH, bicarbonate, chloride, carbon dioxide tension
- Chest X-ray
- Ultrasonography of kidneys and genitourinary tract

Specific situations
- Reticulocyte count, haptoglobin, lactate dehydrogenase
- Creatine phosphokinase
- Complement C3 levels, antistreptolysin
- Antinuclear antibody
- Antineutrophil cytoplasmic antibody
- Antiglomerular basement membrane antibody
- Hepatitis B surface antigen; hepatitis C serology.

Table 3 Urinary indices to distinguish prerenal from intrinsic acute kidney injury

	Prerenal	*Intrinsic renal*
Specific gravity	> 1.020	< 1.010
Urinary osmolality (mOsm/kg)	> 500	< 300
Urine Na (mEq/L)	< 20	> 40
Fractional excretion of sodium (%)	< 1	> 1
Blood urea nitrogen/creatinine	> 20:1	< 20:1

Biomarkers for Early Diagnosis of AKI

Diagnosis of AKI relies on estimation of renal function by serum creatinine level which has many limitations. Serum creatinine concentrations do not change until significant injury and loss of renal function has occurred. Besides, serum creatinine levels can vary with muscle mass and with different methods of measurement used in laboratories. This has led to interest in the discovery and validation of novel AKI biomarkers in serum and urine for early diagnosis and to estimate severity of AKI **(Table 4)**. However, the routine use of the biomarkers in the clinic are limited as they have not been integrated with creatinine and urine output changes to enhance management of AKI. These noninvasive biomarkers of AKI have only been tested in small subsets of the critically ill neonates and hence the utility of these biomarkers has not been established. To ensure judicious use of biomarkers, it is important that children *at risk* for AKI are identified. Renal angina index (RAI) has found to be useful for prediction of severe AKI. The RAI consists of three risk factors (PICU admission, ventilation or use of ionotropes, and organ transplant) and two markers of renal injury (change in GFR from baseline and percent fluid overload) which are assigned points. The score can range from 1 to 40; score more than 8 predicts severe AKI.

MANAGEMENT

Management of AKI includes optimizing renal perfusion pressure and oxygenation and treating associated complications, while ensuring nutrition and avoidance of additional nephrotoxins.

Maintenance of Fluid Balance

Fluid and electrolyte prescription depends on the volume status of the patient. Blood pressure, heart rate, skin turgor, capillary refill and mental status are used to assess the intravascular volume. Children who are severely dehydrated are likely to be in prerenal azotemia. Fluid resuscitation with 10–20 mL/kg normal saline boluses (maximum 60–80 mL/kg) to re-establish intravascular volume is warranted. Further boluses are given if hypovolemia persists. Normal saline is the preferred choice of fluid for volume expansion. Use of artificial colloids like hydroxyethyl starch should

Table 4 Serum and urinary biomarkers in acute kidney injury

	Early detection	*Need for renal replacement therapy*	*Death*
Serum	NGAL, cystatin C, Pro-ANP	NGAL, cystatin C	
Urine	NGAL, IL-18, KIM-1, γ-GT, NAG, MMP-9	NGAL, cystatin C, NAG, KIM-1, α1 microglobulin, β2 microglobulin	NGAL, IL-18, KIM-1

Abbreviations: ANP, atrial natriuretic peptide, γ-GT, glutamyltransferase, IL, interleukin, KIM-1, kidney injury molecule-1, MMP-9, matrix metalloproteinase-9, NAG, N-acetyl-β-d-glucosamide, NGAL, neutrophil gelatinase associated lipocalin.

be avoided as there are indications of an increased risk of AKI. If there is no urine output, furosemide 2 mg/kg IV is given.

Children with prerenal azotemia who do not pass urine after adequate fluid resuscitation or children with normal intravascular volume and oliguria are likely to have intrinsic AKI. The fluids prescribed should be restricted to insensible losses (400 mL/m^2/24 hour) plus replacement of urine output and extrarenal losses (gastrointestinal losses due to diarrhea and vomiting). Children receiving mechanical ventilation require lower insensible loss volume replacement. The replacement of all or only part of extrarenal losses depends on the clinical situation. Urinary and insensible losses are replaced with 0.45% saline and 5% dextrose respectively. Children with fluid overload may be managed with replacement of insensible losses plus replacement of half of urine output and extrarenal losses. Those with overt fluid overload will require dialysis in addition to fluid restriction. Patients with polyuric AKI such as aminoglycoside toxicity are given appropriate fluid and electrolyte replacement based on urine output and serum electrolytes.

Ongoing fluid therapy is guided by daily weights, blood pressure, fluid input and output records, physical examination, nutritional needs of the child and serum electrolytes. In critically ill children, central venous pressure monitoring may be necessary to guide fluid therapy. Attention to fluid balance in critically ill children is necessary to prevent fluid overload, since presence of AKI increases ICU mortality, at least in part due to fluid retention.

Cumulative fluid overload:

$$\frac{\text{Fluid input (L) – fluid output (L)}}{\text{ICU admission weight (kg)}} \times 100$$

If the child has more than 10% fluid overload, evaluation for renal support therapy should occur and if overload is more than 20%, initiation of renal support therapy should be strongly considered. In children with oligoanuric renal failure, potassium containing fluids should not be given unless they are severely hypokalemic.

Treatment of Complications

Hyperkalemia, dysnatremias, hypertension, metabolic acidosis and anemia are complications in children with AKI, which should be recognized and treated promptly **(Table 5)**.

Nutritional Support

Acute kidney injury can be associated with severe anorexia, and child may be at risk for malnutrition when AKI is prolonged. Child

should receive appropriate maintenance calories and proteins. The requirement may be higher in children with hypercatabolic state. If sufficient calories cannot be achieved while maintaining appropriate fluid balance, early initiation of dialysis is considered.

Treatment of Underlying Cause

Prompt recognition and management of underlying cause for AKI is important in limiting the severity of AKI **(Box 3)**.

Pharmacologic Therapy

Diuretics and *renal-dose* dopamine (5 μg/kg/min) are commonly used to prevent or limit AKI. Meta-analyses have confirmed that renal-dose dopamine has no benefit and may even be harmful. The main indication for use of diuretics is management of volume overload. Diuretics may increase the urine output thereby allowing easier management of fluid balance. In absence of fluid overload, the conversion of oliguric to nonoliguric AKI using diuretics does not improve morbidity, mortality, or renal outcomes. While there are no current specific therapy to promote recovery in human AKI (specifically ATN), several potential therapies are being studied (e.g., melanocyte-stimulating hormone, insulin-like growth factor-1 radical scavenger and antioxidants, mesenchymal stem cells, and erythropoietin).

Drug Dosing in Acute Kidney Injury

Prescribing medications in AKI requires attention as many drugs are metabolized and/or excreted by kidneys. The dose and frequency of administration of drugs should be adjusted for the degree of renal failure, based on the GFR (GFR > 50 mL/min/1.73 m^2, 20–50 mL/min/1.73 m^2, or < 20 mL/min/1.73 m^2). Drugs that

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BOX 3 Management of specific causes of acute kidney injury

- Withdrawal, replacement of medication (aminoglycosides, nonsteroidal anti-inflammatory drugs)
- Antimicrobial therapy (malaria, leptospirosis, sepsis, urinary tract infection)
- Surgical intervention for obstruction (removal of stones)
- Diuretics and alkalinization of urine (crush injury, myoglobinuria, hemoglobinuria)
- Plasmapheresis (atypical hemolytic uremic syndrome, rapidly progressive GN, vasculitis)
- Immunosuppression (rapidly progressive GN, vasculitis, autoimmune thrombotic microangiopathy).

Table 5 Management of complications of acute kidney injury

Complication	Treatment
Hypertension	*Symptomatic*: Nitroprusside 1–8 μg/kg/minute infusion; labetalol 0.25–3 mg/kg/hour; furosemide 2–4 mg/kg IV if fluid overload *Asymptomatic*: Nifedipine 0.3–0.5 mg/kg PO
Metabolic acidosis	Sodium bicarbonate (IV, oral) based on severity; refractory acidosis may require dialysis
Hyperkalemia	*Emergency*: Calcium gluconate (10%) 0.5–1 mL/kg over 5–10 minutes Salbutamol 5–10 mg nebulized *Less urgent*: Glucose (50%) 0.5–1 g/kg with 0.1–0.2 units/kg insulin Sodium bicarbonate (8.4%) 1–2 mL/kg over 15–20 minutes Calcium resonium 1 g/kg/dose 8 hours *Refractory:* May require dialysis
Hyponatremia	*Fluid overload*: Restrict fluids *Sensorial alteration or seizures*: 3% saline 5 mL/kg over 30–90 minutes
Hypocalcemia	IV 10% calcium gluconate (1 mL/kg, maximum 10 mL) over 30 minutes under cardiac monitoring
Hyperphosphatemia	Phosphate binders (calcium carbonate, acetate); dietary phosphorus restriction

are nephrotoxic (aminoglycosides, NSAIDs, radiocontrast agents, vancomycin) should be avoided.

Renal Replacement Therapy

The indications to initiate RRT are not absolute and are determined by a number of factors, including the underlying cause, patient age, rapidity of renal failure and fluid and electrolyte abnormalities **(Box 4)**. The goals are to correct metabolic abnormalities, restore and maintain fluid and electrolyte balance, and maintain the physiological milieu. RRT is provided by peritoneal dialysis, intermittent hemodialysis or continuous RRT. These modalities have advantages and limitations, and comparisons of modalities is difficult. The choice of modality is determined by multiple factors: clinical situation, age and patient size, hemodynamic status, availability of resources and expertise, and the cost of therapy.

OUTCOMES

Acute kidney injury is an independent risk factor for mortality with children dying *from* and not just *with* renal failure. The mortality rates in critically ill children with AKI are high, ranging between 10% and 60% with a higher proportion in those with severe AKI and if complicated by multiorgan failure. In addition, 10–25% patients with AKI may develop chronic kidney disease. Children who survive an episode of AKI should be followed-up long-term with monitoring of blood pressure, urinalysis and measurement of serum creatinine. The prognosis of AKI is dependent on the underlying etiology of the AKI. Children with primary renal disease (acute GN, acute interstitial nephritis, diarrhea-related HUS) have lower mortality compared to children who develop AKI due to multifactorial causes (critically ill). ATN due to ischemia or nephrotoxins has favorable outcomes. Prognostic factors include age of the child, duration and severity of anuria and AKI, need for RRT, fluid overload and severity of illness at time of admission.

IN A NUTSHELL

1. Acute kidney injury is an important contributor to mortality and morbidity in critically ill children. Pediatric RIFLE, AKIN and KDIGO criteria are available to define and stage AKI.
2. Volume depletion due to acute gastroentritis, infections like malaria, leptospirosis, dengue and hemorrhagic fever, snake evenomation and HUS are common causes of AKI in children.
3. In critically ill children, causes of AKI include sepsis, multiorgan dysfunction, trauma and organ transplantation.
4. Ultrasonography is a sensitive investigation to identify obstructive cause of AKI.
5. Biomarkers in serum and urine are useful for early diagnosis, but their utility is not been proven.
6. Life-threatening complications are pulmonary edema, hypertensive encephalopathy, hyponatremia, hyperkalemia and severe metabolic acidosis.
7. There are no specific drugs to treat AKI; supportive care is the cornerstone of management.
8. Indications for RRT are not absolute and are determined by a number of factors. RRT may be provided by peritoneal dialysis, intermittent hemodialysis, or continuous RRT.
9. Patients who survive AKI should be followed-up for chronic kidney disease.

MORE ON THIS TOPIC

Ashraf M, Shahzad N, Irshad M, et al. Pediatric acute kidney injury: A syndrome under paradigm shift. Indian J Crit Care Med. 2014;18:518-26.

Bagga A, Sinha A. Acute kidney injury: increasing recognition merits more action. Indian J Pediatr. 2013;80:247-8.

Fortenberry JD, Paden ML, Goldstein SL. Acute kidney injury in children: an update on diagnosis and treatment. Pediatr Clin North Am. 2013;60:669-88.

Gulati A, Bagga A. Acute kidney injury: standardizing terminologies. Indian J Pediatr. 2008;75:526-8.

Kumar G, Vasudevan A. Management of acute kidney injury. Indian J Pediatr. 2012;79:1069-75.

Lameire N. The definitions and staging systems of acute kidney injury and their limitations in practice. Arab J Nephrol Transplant. 2013;6:145-52.

Prowle JR. Acute kidney injury: an intensivist's perspective. Pediatr Nephrol. 2014;29:13-21.

Siew ED, Furth SL. Acute kidney injury: a not-so-silent disease. Kidney Int. 2014;85:494-5.

BOX 4 Indications for renal replacement therapy

1. Fluid overload (pulmonary edema, severe hypertension)
2. Uremia with encephalopathy, bleeding or pericarditis
3. Metabolic derangements, including refractory hyperkalemia, acidosis, hyperphosphatemia
4. *Intoxications:* Lithium, methyl alcohol, salicylates
5. Inborn errors of metabolism: Urea cycle defects

Chapter 41.12
Renal Replacement Therapy for Acute Kidney Injury
Sidharth Kumar Sethi, Rupesh Raina

Provision of renal replacement therapy (RRT) to children requires special considerations as compared to adult patients. The weight varies from a few hundred grams in extremely low birthweight babies to over 100 kg in obese adolescents. The etiology of acute kidney injury (AKI) varies (*See* Chapter 41.11). Optimal care of the patients with severe AKI involves an understanding of the features of multiorgan dysfunction syndrome, and the local availability of RRT modalities and expertise.

INDICATIONS

Multiple retrospective studies in critically ill children have that AKI and multiorgan dysfunction syndrome develop early and are associated with increased mortality and prolonged ICU stay. Early provision of RRT in these children may prevent life-threatening complications of uremia, fluid overload and dyselectrolytemia. Indications of RRT are listed in previous chapter. However, these criteria are relatively late manifestations of renal dysfunction, and most physicians are inclined to initiate RRT relatively early in critically sick children. Information from prospective series show that fluid overload in critically ill children is an independent predictor of mortality. Early initiation of RRT also provides room for parenteral nutrition and/or blood products while preventing fluid overload.

CLASSIFICATION

The available modalities for RRT function chiefly using one or more of the following physiological mechanisms: (1) Diffusion: Solute exchange across a semipermeable membrane, governed principally by concentration gradient, solute size and charge; (2) Ultrafiltration: Movement of water across a membrane primarily by hydrostatic pressure (in hemodialysis and hemofiltration) or along an osmotic agent (peritoneal dialysis); and (3) Convection: Solute transfer along with ultrafiltration across a semipermeable membrane, occurring independent of the concentration gradient. Various modalities for RRT are classified on the basis of these mechanisms. Based on the duration, therapies are classified as intermittent or continuous, where duration of each intermittent therapy is less than 24 hours, whereas for continuous therapy is at least 24 hours. Hemodialysis is an intermittent therapy, even when prolonged beyond the standard 4 hours prescription, as during sustained low efficiency dialysis and extended daily dialysis.

CHOICE OF MODALITY

The choice of dialysis modality depends on patient and organizational characteristics.

Patient Characteristics

Desired goal of dialysis If the patient just requires fluid removal, any of the modalities, including peritoneal dialysis, hemodialysis or slow continuous ultrafiltration may be used, based on the child's hemodynamic status and institutional preferences.

Size Putting a double lumen hemodialysis catheter in neonates may be technically difficult and not achieve adequate flows. In these situations, peritoneal dialysis is a viable option.

Urgency of solute clearance Conditions associated with rapid solute generation and need for urgent fluid removal, such as tumor lysis syndrome, hyperammonemia, symptomatic hyperkalemia and ingestion of a dialyzable toxin, are indications where relatively efficient modalities like hemodialysis or continuous RRT (CRRT) are preferred over peritoneal dialysis.

Hemodynamic status CRRT may be the only suitable options for critically ill children with sepsis and multiorgan dysfunction with shock requiring inotropes; postoperative infants, e.g., following cardiopulmonary bypass, may be managed on peritoneal dialysis.

Coexistent coagulopathy: Attainment of vascular access and use of anticoagulation for hemodialysis or CRRT are risky in presence of prolonged bleeding or prothrombin time or thrombocytopenia.

Organizational Characteristics

Peritoneal dialysis is preferred in resource constrained areas, while hemodialysis or CRRT are used as primary modalities in units with available expertise. The preference may depend on the finances, unit preference or staff training and expertise.

Peritoneal Dialysis

Peritoneal dialysis is the most widely used RRT in the world, especially in centers with limited resources. Because of its simplicity, safety and relative ease, the procedure can be performed in very small patients. The technique has minimal serious hemodynamic consequences and does not require vascular access, often the limiting factor in initiating dialysis in small infants.

Catheters

Catheters used commonly for acute dialysis in infants and children are the noncuffed rigid acute catheter and the surgically placed cuffed silicone Tenckhoff catheter. Once inserted, a stiff catheter can be used safely for a maximum of 72 hours, beyond which there is an increasing risk of peritonitis. Tenckhoff catheters are preferred when anticipating prolonged dialysis.

Prescription

The prescription of dialysis is individualized to the clinical situation. The volume of dialysis fluid infused into the peritoneal cavity is adjusted to the body size. In children, the peritoneal surface area is related more to body surface area than to weight and the infused volume is typically 800–1,100 mL/m^2, starting with lower volumes. The exchange time is 1 hour (inflow 10 minutes, dwell 30 minutes, outflow 20 minutes). In children with fluid overload and hyperkalemia, the dialysate fluid used may be hypertonic (2.5–3%) and with shorter cycles. The duration of dialysis depends on the patient's requirement.

Complications

Leakage, poor drainage and ultrafiltration are commonly encountered. Peritonitis is a constant threat, especially if the catheter has been manipulated. Peritonitis during acute peritoneal dialysis is managed with intraperitoneal or intravenous antibiotics; catheter removal is required if a stiff catheter was used or response to therapy is inadequate at 48–72 hours.

Contraindications

Contraindications to dialysis include recent abdominal surgery, necrotizing enterocolitis and presence of a ventriculoperitoneal shunt, because of the risk of peritonitis.

Hemodialysis

Hemodialysis is the most efficient method of RRT, accomplishing solute transfer and ultrafiltration at high rates. It is effective in acute

settings in management of volume overload, intoxication, tumor lysis syndrome or hyperammonemia. It is not suited for patients with hemodynamic instability or bleeding tendency and in small infants where vascular access is difficult to establish.

Vascular Access

Acute vascular access for hemodialysis is most often accomplished by placing a double lumen catheter in the internal jugular or femoral vein. These sites provide adequate blood flow and are acceptable for short-term use in the hospitalized patient. Due to the risk of soiling, femoral access should only be used in emergency situations.

Dialyzers

The size of the dialyzer depends upon body size, with the dialyzer area approximating the patient surface area. Newer generation dialysis membranes constructed from materials such as polysulfone and polymethylmethacrylate cause less proinflammatory cytokine activation.

Prescription

The prescription takes into account the extracorporeal blood volume in dialyzer and tubings, rates of blood and countercurrent dialysate flow and the desired duration and ultrafiltration. Heparin is the preferred anticoagulant; saline flushes are used to prevent clots in the circuit if heparin is contraindicated by bleeding diathesis. Based on relative ratio of body size and volume in tubings, the circuit may require priming with blood, saline or 5% albumin. The ultrafiltration achieved through dialysis depends on the hemodynamic status of the child.

Complications

Hypotension, leg cramps, abdominal pain and vomiting may result from excessive ultrafiltration or dyselectrolytemia. Problems related to vascular access, such as thrombosis, stenosis, and infection, may require catheter removal.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy (RRT) is defined as any extracorporeal blood purification therapy intended to substitute for acutely impaired renal function over an extended period of time and prescribed continuously for more than 24 hours. CRRT is classically used to refer to continuous venovenous hemofiltration, continuous venovenous hemofiltration with dialysis or a combination of convective and diffusive clearance, as in continuous venovenous hemodiafiltration. CRRT is the preferred modality in sick patients in pediatric intensive care units. It mimics the functioning in a normal kidney where solute and fluid are continuously removed. CRRT is more precise in solute and fluid removal than peritoneal dialysis, and is tolerated by sick children with hypotension requiring multiple inotropes.

Issues related to vascular access in CRRT are the same as for hemodialysis. Heparin has been used as bolus or infusions; regional anticoagulation using citrate or no anticoagulation (saline flushes) may also be used. A replacement solution, typically bicarbonate based, is required. Blood and dialysate flow rates are considerably lower as compared to hemodialysis. The ultrafiltration targets are titrated to the fluid balance and hemodynamic status and choice between convective and diffuse modality is based on physician preference. While convective clearance theoretically achieves removal of cytokines and toxins, any modality may be used for small molecule clearance. CRRT requires to be carried out in an intensive care unit for close supervision. The chief disadvantages are its cost, the need for technical expertise and equipment, and risk of hemorrhage in critically sick children.

OUTCOMES

Currently there are no randomized trials comparing clinical outcomes of the various dialysis modalities in children. Results of a study in adult patients failed to show benefit in survival from early versus late initiation of RRT. Timely initiation of RRT for AKI in children with fluid overload and sepsis is considered useful in enabling recovery. Retrospective studies suggest that patient survival is predicted by underlying diagnosis and hemodynamic stability, and the severity of illness is more closely associated with risk of mortality than the choice of RRT.

IN A NUTSHELL

1. Early provision of RRT in AKI may prevent life-threatening complications of uremia, fluid overload and dyselectrolytemia.
2. The available modalities for RRT include hemodialysis and peritoneal dialysis.
3. Hemodialysis is intermittent therapy, even when prolonged beyond the standard 4 hours prescription.
4. Continuous RRT is defined as any extracorporeal blood purification therapy intended to substitute for acutely impaired renal function over an extended period of time and prescribed continuously for more than 24 hours.
5. Timely initiation of RRT for AKI in children with fluid overload and sepsis is considered useful in enabling recovery.

MORE ON THIS TOPIC

Bridges BC, Askenazi DJ, Smith J, Goldstein SL. Pediatric renal replacement therapy in the intensive care unit. Blood Purif. 2012;34:138-48.

Fortenberry JD, Paden ML, Goldstein SL. Acute kidney injury in children: an update on diagnosis and treatment. Pediatr Clin North Am. 2013;60:669-88.

Goldstein SL. Advances in pediatric renal replacement therapy for acute kidney injury. Semin Dial. 2011;24:187-91.

Sethi SK, Bunchman T, Raina R, Kher V. Unique considerations in renal replacement therapy in children: Core curriculum 2014. Am J Kidney Dis. 2014;63:329-45.

Sutherland SM, Alexander SR. Continuous renal replacement therapy in children. Pediatr Nephrol. 2012;27:2007-16.

Chapter 41.13
Hemolytic Uremic Syndrome
Aditi Sinha, Arvind Bagga

Hemolytic uremic syndrome (HUS) is a heterogeneous group of disorders characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency. Histologically, thrombi occlude blood vessels in the micro-vasculature, termed thrombotic microangiopathy (TMA). While the disease is uncommon (incidence 0.7–8 cases/100,000 population/year), it is an important cause of acute kidney injury (AKI) in children and the most common cause of childhood AKI requiring dialysis.

ETIOLOGY

Conditions that result in HUS are listed in **Table 1**. Broadly, two forms are recognized. *Shiga toxin-associated HUS* is more common, occurs in young children and is associated with shiga toxin-producing enteropathogens, typically *Escherichia coli* O157:H7 or *Shigella dysenteriae*. *Atypical HUS* (aHUS) refers to HUS not caused by shiga toxin, and comprises diverse conditions including abnormalities in regulation of the complement cascade, cobalamin pathway and deficiency of von Willebrand protease, a metalloproteinase with thrombospondin motifs 13 (ADAMTS13). HUS may follow precipitating events like infections, drugs, transplantation, pregnancy and autoimmune conditions, termed *secondary aHUS*.

Shiga Toxin-associated Hemolytic Uremic Syndrome (STEC-HUS)

Diarrhea or dysentery due to shiga toxin-producing *E. coli* (STEC) (chiefly O157:H7; O104:H4 in a recent epidemic in west Europe)

Table 1 Classification of hemolytic uremic syndrome and related disorders

Infection induced
• *Shiga and verotoxin-producing bacteria:* Enterohemorrhagic *E. coli*; *S. dysenteriae* type 1
• Invasive infection with *Streptococcus pneumoniae*
• *Other bacterial infections: Citrobacter*, *Salmonella*, *Campylobacter*, *Bartonella*
• *Viruses:* Coxsackievirus, echovirus, influenza, varicella, HIV, Epstein-Barr virus
Disorders of complement regulation
• Inherited disorders of complement regulation
• Acquired disorders of complement regulation; antibodies to complement factor H
von Willebrand protease (ADAMTS13) deficiency
• Inherited deficiency of ADAMTS13 (Upshaw-Schulman syndrome)
• *Acquired ADAMTS13 deficiency:* Autoimmune; drug-induced
Defective cobalamin metabolism
Drug induced
Quinine, mitomycin, ticlopidine, clopidogrel, calcineurin inhibitors, oral contraceptives
Other causes

ADAMTS13 a metalloproteinase with thrombospondin motifs 13.

or *Shigella dysenteriae 1* (in Asia and Africa) is followed by HUS in about 10–15% cases. The incidence is highest in children below 5-year-old, at 6 per 100,000 per year. Shiga toxin-mediated injury chiefly targets endothelia with globotriaosylceramide 3 (Gb3) receptors, found in kidneys, brain, liver, pancreas and heart. The risk of HUS is high for certain strains (e.g., O104:H4) and infection with shiga toxin 2 (rather than shiga toxin 1) producing organisms, and use of quinolones within 3 days of infection. Interference with protein synthesis incites cytokine production and increased expression of adhesion molecules on endothelial cells, triggering coagulation and fibrin deposition in the microvasculature, with sequestration of red cells and platelets. TMA in STEC-HUS predominantly affects glomeruli.

Atypical HUS

Atypical HUS is uncommon (prevalence 2–7 per million children), and has a chronic and relapsing course and risk of end stage renal disease (ESRD). While distinguished from classic HUS by absence of diarrheal prodrome, the disease is often triggered by febrile, respiratory and even diarrheal infections. Microangiopathy affects interlobular arteries and result in severe hypertension and progressive renal insufficiency. Predisposing factors include abnormalities in complement regulation, infection with pneumococci, cobalamin deficiency, lupus and medications (cyclosporin, mitomycin) **(Table 1)**.

CLINICAL FEATURES

Shiga Toxin-associated HUS (STEC-HUS)

Within a week of profuse and usually bloody diarrhea (hemorrhagic colitis), patients develop fatigue, pallor and oligoanuria, with or without fluid overload, hypertension and edema. Most patients have mild disease managed with fluid restriction, nutrition support and control of hypertension. However, severe cases with anuria often require dialysis, and may show signs of extrarenal involvement, chiefly brain and pancreas, and uncommonly liver or heart. Cerebral involvement, manifest as irritability, altered consciousness and seizures, is noted in 3–50% cases.

Atypical Hemolytic Uremic Syndrome

The onset may be insidious or present with a rapidly progressive illness. Important clinical characteristics of patients with various forms of aHUS are summarized in **Table 2**. Based on age, the following etiologies are suspected: (1) less than 6-month-old: hereditary ADAMTS13 deficiency, methylmalonic aciduria; (2) infants and young children: STEC-HUS, *S. pneumonia*-associated HUS, complement factor H deficiency, mutations in diacylglycerol kinase ε (DGKE*)*; (3) school age children and adolescents: anticomplement factor H (anti-CFH) antibody-mediated HUS, CD46 deficiency, autoantibodies against ADAMTS13.

DIAGNOSIS

The diagnosis of HUS is based on documentation of azotemia, thrombocytopenia (platelets < 150,000/mm^3) and hemolysis, occurring with or without history of preceding diarrhea or dysentery. Hemolysis is identified as anemia, microangiopathy (fragmented RBC) on peripheral smear, reticulocytosis and increased lactate dehydrogenase; neutrophilic leukocytosis is seen in patients with shigellosis. Blood levels of urea and creatinine reflect the severity of renal failure. Urine sediment may be normal

Table 2 Common causes of atypical hemolytic uremic syndrome (aHUS)

Abnormal or deficient factor	Function	% of aHUS*	Minimum age	Low C3, %	ESRD^, %	Relapses, %	Post-transplant recurrence, %
C3	Central role in the complement cascade; substrate for C3 convertase; active form C3b is required for enzymatic complexes	2–10	> 1-year	70–80	60	50	40–70
Complement factor H	Binds C3b as cofactor for CFI-mediated cleavage to inactive iC3b; has decay accelerating activity for C3 convertase	20–30	< 1-month	30–50	50–70	50	75–90
Complement factor I	Serine protease; requires a cofactor to cleave C3b or C4b	4–10	< 1-month	20–30	50	10–30	60–80
Membrane cofactor protein or CD46	Binds C3b and C4b and has cofactor activity for both ligands	5–15	> 12-months	0–27	0–10	70–90	< 20
Complement factor B	Provides catalytic site for the C3 convertase	1–4	< 12-months	100	50	3/3	100
Anti-CFH antibody	Binds to factor H to reduce its cell surface complement regulatory activity	6–25	5–15 years	40–60	30–40	20–50	Low
Thrombomodulin	Accelerates CFI-mediated inactivation of C3b in presence of cofactors; helps inactivate C3a and C5a	3–5	1-month	50	50	30	NA
Diacylglycerol kinase ε	Not linked directly to the complement cascade; hypothetically causes a prothrombotic state	25–30% of < 1-year	< 12-months	Low C3 in 1 report	80–100	Yes; NA	NA

*No abnormality detected in ~40% cases.
^Or death within 1 year from onset.
Abbreviations: ESRD, end stage renal disease; NA, not available; CFI, complement factor I.

or show red cells and non-nephrotic range proteinuria. Coombs' test is positive in *S. pneumoniae*-associated HUS.

Table 3 lists important investigations in patients of HUS, including those to identify the underlying etiology. The diagnosis of STEC-HUS should be considered in patients older than 6 months with history of diarrhea or dysentery in the preceding 2 weeks. Establishing etiology requires either stool culture or polymerase chain reaction for shiga toxin; in those presenting late, serological response to bacterial lipopolysaccharide may be determined. Diagnosis of defect in cobalamin metabolism requires levels of plasma and urine homocysteine and methylmalonic acid.

Several patients with atypical HUS show low levels of complement C3 suggesting complement dysregulation; these patients require detailed analysis of components and regulators of the complement pathway. However, normal C3 does not exclude a complement disorder and 30–50% patients with complement dysregulation have normal C3 levels. Samples for complement studies should be taken before plasmapheresis or infusing blood products **(Flow chart 1)**. Facilities for complement studies are available in research laboratories, including at the All India Institute of Medical Sciences, New Delhi (details at *www.ispn-online.org*).

Histology

Histological features include intimal hyperplasia with thickening of arterioles and capillaries, endothelial swelling and detachment, subendothelial widening due to accumulation of cell debris, thrombi in vessel lumina and mesangiolysis **(Figs 1A and B)**. Patchy or extensive renal cortical necrosis may be seen. The lesions progress to glomerular sclerosis, interstitial fibrosis and tubular atrophy. Similar changes may be present in the brain, heart, lungs, pancreas and the gastrointestinal tract.

MANAGEMENT

General management focuses on supportive care. This includes attention to fluid and electrolyte balance, management of hypertension, monitoring for extrarenal involvement, nutritional support and provision of renal replacement therapy as required. Most children develop some renal insufficiency and approximately two-thirds require dialytic support. Patients with severe anemia may need packed red cells. Platelet transfusions are limited to children with active bleeding since they might increase risk of microthrombi.

STEC-Hemolytic Uremic Syndrome

There is no specific treatment for STEC-HUS, with current management focusing on best supportive therapy and avoiding antidiarrheal drugs. While used anecdotally in patients with severe neurological symptoms or refractory hemolysis, current evidence does not support the use of antibiotics, plasma exchange, immunoadsorption, shiga toxin-binding agents and complement inhibition (eculizumab) to ameliorate the disease course.

Atypical Hemolytic Uremic Syndrome

While there are no evidence-based guidelines on therapy, there is consensus on the need for prompt plasmapheresis or plasma exchanges, which forms the standard of care for patients with atypical or recurrent HUS. Patients with antifactor H antibodies benefit from additional use of immunosuppression to reduce

Table 3 Evaluation in patients with hemolytic uremic syndrome

- *Renal function tests*
- Complete blood counts with peripheral smear; schistocytes; reticulocyte count
- Direct Coombs test
- Lactate dehydrogenase, haptoglobin
- Complement C3
- *Urinalysis:* Proteinuria; hematuria

Based on suspected etiology

Shiga toxin-mediated HUS
- Stool or rectal swab culture
- Polymerase chain reaction for shiga toxin in stool
- Serum antibodies to lipopolysaccharide

Atypical HUS
- Complement factors H, I (ELISA)
- Membrane cofactor protein or CD46 (Flow cytometry)
- Antifactor H antibodies (ELISA)
- Sequencing for complement factors H, I, B, C3, CD46 and DGKE
- MLPA for CFHR1-5; CFH (copy number variation)

Streptococcus pneumoniae associated
Direct Coombs' test, blood culture, positive T-antigen (peanut agglutination)

Defective cobalamin metabolism
- Serum homocysteine, methionine (high performance liquid chromatography)
- Urine methylmalonic acid (tandem mass spectrometry)
- Urine and plasma organic acid chromatography
- Sequencing for *MMACHC* (gene for methylmalonic aciduria and homocystinuria type C)

Thrombotic thrombocytopenic purpura
ADAMTS13 activity, ADAMTS13 antigen, anti-ADAMTS13 antibodies

Secondary HUS
- Antinuclear antibodies; antiphospholipid antibodies, antineutrophil cytoplasmic antibodies
- Antibodies to human immunodeficiency virus
- Polymerase chain reaction for cytomegalovirus, Epstein-Barr virus

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CFHR, complement factor H related; DGKE, diacylglycerol kinase ε; MLPA, multiplex ligation-based probe amplification; ELISA, enzyme-linked immunosorbent assay; CFH, complement factor H.

Flow chart 1 Proposed algorithm for evaluation of patients with hemolytic uremic syndrome

Hemolytic uremic syndrome

Diarrheal	Atypical*	Secondary
Shigatoxin, stool culture Complement C3	Factor H, C3 anti-CFH, MCP CFHR1/3 deletion Mutation studies	Medications HIV Post-transplantation Malignancy
Supportive care *Severe illness:* Plasma exchanges or infusions	Supportive care Plasma exchange Immunosuppression if anti-CFH	
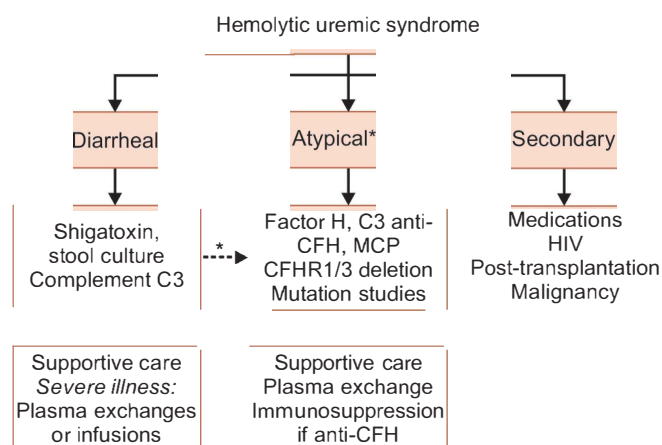
*Consider atypical HUS, if less than 6 months; nondiarrheal trigger, low C3, relapses or family history.
Abbreviations: MCP, membrane cofactor protein; CFH, complement factor H; CFHR, CFH related.
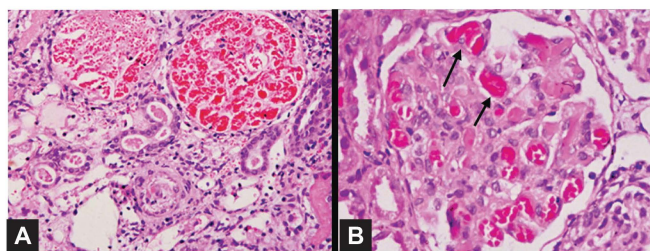
Figures 1A and B Features of thrombotic microangiopathy showing (A) Severe mesangiolysis; (B) Glomerulus with endothelial swelling and capillary lumina occluded with fibrin thrombi

antibody production. The use of eculizumab, a high affinity monoclonal antibody targeted against C5, is reported to benefit patients with HUS associated with activation of the complement cascade.

Plasmapheresis (Plasma Exchange)

Plasma exchanges are expected to replace absent or mutated complement regulators and/or remove circulating anti-CFH antibodies. Plasma exchanges should begin as soon as possible, preferably within 24 hours of the diagnosis of aHUS, without awaiting biopsy diagnosis or results of complement studies. Most centers perform 1.5 volume exchanges daily for 5 days or until hematological remission (platelets > 150,000/mm^3; no hemolysis), followed by 4–6 plasma exchanges each on alternate days, twice weekly and eekly.

Eculizumab

This high affinity monoclonal antibody against C5 blocks terminal complement activation. This agent is emerging as the standard of car for patients with atypical HUS. Eculizumab is preferred in patients with unsatisfactory response to 3–5 days' plasmapheresis and inability to perform plasmapheresis, due to difficult vascular access or other complications. The medication is expensive, and not available in India.

Monitoring

Patients should be monitored for hematological remission and for renal dysfunction, proteinuria and hypertension at follow-up. Patients with atypical HUS should be screened for relapses, particularly following infections. Outcome of STEC-HUS is satisfactory, with resolution of renal impairment over a few weeks. Twenty to thirty percent cases have residual renal defects, ranging from proteinuria and hypertension to ESRD. Oligoanuria persisting for more than 4 weeks, cerebral involvement and cortical necrosis are associated with adverse prognosis. The long-term prognosis for patients with atypical HUS is guarded, with acute mortality of 25% and progression to ESRD in 50%. An unsatisfactory outcome is predicted in those with mutations in genes encoding CFH or CFI. Those with anti-CFH antibodies respond to plasma exchange and immunosuppression. Patients with abnormalities in CD46 are less likely to respond to plasma exchange and show relapses.

Renal transplantation is associated with 50% rate of recurrence in the allograft. The risk is high in patients with mutations in CFH or CFI, with 80% patients losing their graft, in contrast to mutations in CD46 where post-transplant recurrence is rare. Combined liver kidney transplantation or the use of eculizumab is recommended in the former. Patients with autoantibody-associated HUS requiring transplantation may need plasma exchanges and immunosuppressive therapy before and during transplantation.

MORE ON THIS TOPIC

Ariceta G, Besbas N, Johnson S, European Pediatric Study Group for HUS. Guideline for the investigation and initial therapy of diarrhea negative hemolytic uremic syndrome. Pediatr Nephrol. 2009;24:687-96.

Besbas N, Karpman D, Landau D, et al. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int. 2006;70:423-31.

Kavanagh D, Goodship TH, Richards A. Atypical hemolytic uremic syndrome. Semin Nephrol. 2013;33:508-30.

Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60.

Verhave JC, Wetzels JF, van de Kar NC. Novel aspects of atypical haemolytic uraemic syndrome and the role of eculizumab. Nephrol Dial Transplant. 2014;29:131-41.

IN A NUTSHELL

1. While HUS is a rare disease, it is an important cause of AKI in children and the most common cause of childhood AKI requiring dialysis.
2. Infection with shiga toxin-producing *E. coli* or *S. dysenteriae* is the chief cause of HUS; therapy is chiefly supportive and outcomes are satisfactory.
3. Abnormalities in complement regulation, secondary to mutations or presence of inhibitory autoantibodies, constitute an important cause of atypical HUS.
4. Apart from supportive therapy, specific treatment for patients with atypical HUS comprises of eculizumab and/or the use of plasma exchanges; immunosuppression is offered to patients with autoantibodies to complement factor H.

Chapter 41.14
Renal Tubular Acidosis
Arvind Bagga, Aditi Sinha

Renal tubular acidoses (RTAs) are transport defects secondary to reduced proximal tubular reabsorption of bicarbonate (HCO_3^-), distal secretion of protons (hydrogen ion, H^+) or both, resulting in impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis, in the absence of significant decrease in glomerular filtration rate (GFR).

PATHOPHYSIOLOGY AND ETIOLOGY

The proximal renal tubule is the chief site of solute and water reabsorption in the nephron. Approximately 60% of the filtered sodium (Na^+) is reabsorbed in the proximal segments, along with water, potassium (K^+), HCO_3^-, phosphate, amino acids and low molecular weight proteins. In contrast, the distal tubule has an important role in the final urine concentration and pH. Specialized transporters are involved in the regulation of Na^+ and K^+ reabsorption and H^+ secretion. Figures 4 and 5 (in Chapter 41.1) illustrate the mechanisms for HCO_3^- absorption in the proximal tubule, and H^+ secretion by the distal tubule. While intercalated cells of the cortical collecting duct are involved in H^+/HCO_3^- transport, principal cells mediate Na^+/K^+ exchange under influence of mineralocorticoids. Na^+ transport by principal cells creates a lumen-negative transepithelial potential that promotes H^+ secretion by intercalated cells. Based on mechanisms and site of dysfunction, RTAs are classified as proximal (type 2) RTA, distal (type 1) RTA and type 4 RTA.

Proximal Renal Tubular Acidosis

The primary defect is bicarbonaturia due to reduced renal threshold for HCO_3^- excretion. Proposed mechanisms include deficient carbonic anhydrase on the brush border, and defective pump secretion or function of the Na^+/HCO_3^- cotransporter, H^+ ATPase, Na^+/H^+ antiporter and the Na^+/K^+ ATPase. However, proximal RTA rarely represents an isolated defect and is more commonly a part of generalized proximal tubular dysfunction, termed Fanconi syndrome, characterized by tubular proteinuria and aminoaciduria and variable degrees of bicarbonaturia, phosphaturia, electrolyte wasting and glucosuria. **Box 1** lists conditions associated with proximal RTA, including known genetic defects and secondary conditions.

Distal Renal Tubular Acidosis

This is characterized by metabolic acidosis secondary to decreased secretion of H^+ ions, resulting in lower values for titratable acidity and NH_4^+ secretion than required to keep pace with daily acid production. In hypokalemic distal RTA (classic RTA or type 1 RTA), urine pH cannot reach maximal acidity (i.e., remains > 5.3) despite systemic acidemia indicating low H^+ concentration in the collecting duct. The condition is secondary to either a secretory (rate) defect or a gradient (permeability) defect. In the former, the rate of secretion of H^+ is low for the degree of acidosis, e.g., secondary to defective function of H^+ ATPase, H^+/K^+ ATPase, or the Cl^-/HCO_3^- exchanger. The gradient (permeability) defect is characterized by an appropriate rate of H^+ secretion but an increased backleak, resulting in dissipation of the pH gradient. Hypokalemia, a common finding in patients with distal RTA, is attributed to increased tubular losses of K^+ that are enhanced by aldosterone stimulation following urinary Na^+ losses and volume

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BOX 1   Etiology of proximal renal tubular acidosis (RTA)

Inherited defects (mutated gene; encoded protein)
- Isolated proximal RTA
  – Autosomal recessive type (*SCL4A4*; sodium bicarbonate cotransporter 1)[*]
  – Autosomal dominant type (unknown)
- Multiple tubular dysfunction (Fanconi syndrome)
  – Isolated Fanconi syndrome, autosomal dominant type (unknown)
  – Isolated Fanconi syndrome, autosomal recessive type (unknown)
  – Dent's disease (*CLCN5*; renal chloride channel)
  – Cystinosis (*CNS*; cystinosin)
  – Tyrosinemia type 1(*FAH*; fumarylacetoacetate hydrolase)
  – Fanconi-Bickel syndrome (*GLUT2/SLC2A2*; glucose transporter GLUT2)
  – Wilson's disease (*ATP7B*; copper-transporting polypeptide ATPase)
  – Galactosemia (*GALT*; galactose-1-phosphate uridylyltransferase)
  – Hereditary fructose intolerance (*ALDOB*; fructose-1-phosphate aldolase)
  – Lowe syndrome (*OCRL1*; phosphatidylinositol-4,5-bisphosphate-5-phosphatase)
  – Glycogen storage disease type 1 (*G6Pa*; glucose-6-phosphatase-alpha)
  – Multiple phenotypes (mitochondrial genes; various mitochondrial enzymes)
- Combined defect in proximal and distal acidification (type III RTA)
  – Associated with osteopetrosis and deafness (*CA2*; carbonic anhydrase type II)

Acquired defects
- Isolated proximal RTA
  – Carbonic anhydrase inhibitors (acetazolamide)
- Multiple tubular dysfunction (Fanconi syndrome)
  – Primary hyperparathyroidism
  – Sjögren syndrome
  – Vitamin D-dependent rickets
  – Paroxysmal nocturnal hemoglobinuria
  – Acute tubulointerstitial nephritis with uveitis syndrome
  – Drugs: ifosfamide, valproate, aminoglycosides, cisplatin
  – Heavy metals and toxins: lead, cadmium, mercury, toluene (glue sniffing)

[*]*Associated with ocular and dental enamel defects, impaired intelligence and basal ganglia calcification.*

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contraction. Hypercalciuria and hyperphosphaturia occur due to the release of calcium phosphate from bone in order to buffer excess H^+ during acidosis, and the direct effects of acidosis on tubular reabsorption of these ions. Hypocitraturia results from citrate utilization in proximal tubular cells, and due to the high luminal pH favoring conversion of citrate^{3-} to the readily reabsorbable citrate$^-$. *Incomplete distal RTA* refers to milder variants of classic distal RTA in which defective tubular H^+ secretion does not lead to systemic acidosis, since daily acid excretion is enabled by enhanced ammoniagenesis. Important etiologies of distal RTA are listed in **Box 2**.

Distal RTA with hyperkalemia may occur due either to (1) voltage defect caused by insufficient negative intratubular potential at the level of cortical collecting duct (hyperkalemic distal RTA); or (2) rate defect due to aldosterone deficiency or resistance (type 4 RTA). The voltage defect leads to reduced secretion of H^+ and K^+, decreased trapping and excretion of NH_4^+ and hyper- or normokalemia. Apart from the latter finding, the voltage defect resembles classic distal RTA.

Type 4 Renal Tubular Acidosis

Characterized by hyperkalemic acidosis and intact ability to lower urine pH, the condition is caused by aldosterone resistance or deficiency **(Box 3)**. Aldosterone increases Na^+ absorption, resulting in a negative intratubular potential, increases urinary K^+

Inherited defects (mutated gene; encoded protein)

- Isolated distal RTA
  - Autosomal dominant type (*SCL4A1*; anion exchanger 1, AE1)
  - With hemolytic anemia; autosomal recessive (*SCL4A1*; AE1)
  - With early hearing loss; autosomal recessive (*ATP6V1B1*; B1 subunit of H^+ ATPase)
  - With normal hearing or delayed hearing loss; autosomal recessive (*ATP6V0A4*; A4 subunit of H^+ ATPase)
- Combined defect in proximal and distal acidification (type III RTA)
  - Associated with osteopetrosis and deafness (*CA2*; carbonic anhydrase type II)

Acquired defects

- Systemic lupus erythematosus
- Sjögren syndrome
- Sickle cell anemia
- Obstructive uropathy
- Reflux nephropathy
- Nephrocalcinosis
- Amphotericin B toxicity.

BOX 3 Etiology of type 4 (hyperkalemic) renal tubular acidosis

Inherited defects (mutated gene; encoded protein)

- Congenital adrenal hyperplasia; autosomal recessive (*CYP21*; 21 hydroxylase aldosterone synthase or P450c21; *CYP11B2*; aldosterone synthase)
- Pseudohypoaldosteronism (PHA); autosomal dominant (*NR3C2*; mineralocorticoid receptor)
- PHA; autosomal recessive (*SCNN1B*; epithelial sodium channel)
- PHA type 2 or Gordon syndrome; autosomal recessive (*PHA2B, PHA2C*; WNK1, WNK4)

Acquired defects

- Aldosterone deficiency without renal disease
  - Addison disease
  - Isolated aldosterone deficiency
  - Adrenal tuberculosis; necrosis
- Aldosterone deficiency in chronic renal insufficiency
  - Obstructive uropathy
  - Interstitial nephritis
  - Nephrocalcinosis
- Aldosterone resistance
  - Post-transplantation
  - *Drugs:* Amiloride, spironolactone, angiotensin-converting enzyme (ACE) inhibitors, heparin, nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors.

losses by enhancing membrane permeability to K^+ and stimulating the basolateral $Na^+/K^+/ATPase$, and directly stimulates the proton pump [Fig. 5 (in Chapter 41.1)]. Aldosterone deficiency or resistance causes hyperkalemic metabolic acidosis. The net H^+ excretion is decreased due to inhibition of ammoniagenesis by hyperkalemia. Although maximally acidic urine (pH < 5.3) can be formed, indicating the ability to establish a maximal H^+ gradient, ammonium excretion is low resulting in positive anion gap.

CLINICAL FEATURES

The most common symptom of tubular dysfunction is poor growth. Additional features that suggest RTA include polyuria, polydipsia, preference for savory foods, refractory rickets and recurrent episodes of dehydration, fever and constipation. Polyuria is caused by osmotic diuresis due to presence of excessive solutes in the tubules and impaired urinary concentration due to persistent hypokalemia.

Proximal Renal Tubular Acidosis

These children present with stunted growth, and/or irritability, anorexia and listlessness. Rickets is unusual in isolated proximal RTA but is common in Fanconi syndrome due to the associated hypophosphatemia. While symptoms related to hypokalemia (e.g., weakness, paralysis) are uncommon, hypokalemia and consequent polyuria are often present in Fanconi syndrome. Nephrocalcinosis and urolithiasis are not seen except with Dent's disease and Lowe syndrome. All children with proximal RTA require evaluation for Fanconi syndrome, including secondary forms **(Box 1)**.

Distal Renal Tubular Acidosis

Features include failure to thrive, polyuria, refractory rickets, and symptoms of hypokalemia, including muscle weakness, neck flop and even paralysis. Hypercalciuria, hypocitraturia and high urine pH contribute to occurrence of calcium phosphate stones. Incomplete forms of distal RTA are suspected in patients presenting with nephrocalcinosis or nephrolithiasis without systemic acidosis; diagnosis is made on demonstrating hypercalciuria and inability to lower urinary pH when acidosis is induced pharmacologically. In children, distal RTA is almost always primary; few have early or delayed sensorineural deafness or ovalocytosis and hemolytic anemia. Presentation in later childhood should prompt evaluation for systemic lupus or Sjögren syndrome.

Type 4 Renal Tubular Acidosis

Findings of the underlying disease (hypoaldosteronism or resistance to action of aldosterone) predominate over features of tubular acidosis. There is nephrocalcinosis or urolithiasis and bone disease is rare. Advanced tubulointerstitial diseases leading to mineralocorticoid resistance should be suspected, particularly in older children. Aldosterone unresponsiveness, associated with obstructive uropathy, is more common than aldosterone deficiency. Patients with pseudohypoaldosteronism (PHA) type 1 present with salt wasting, hyperkalemia and metabolic acidosis with high levels of plasma renin and aldosterone. Patients with PHA type 2 show hypertension, metabolic acidosis, hyperkalemia and suppressed plasma renin activity.

DIFFERENTIAL DIAGNOSIS

Metabolic acidosis may result from extrarenal processes, which result in either increased endogenous acid synthesis (e.g., ketoacidosis) or enhanced HCO_3^- losses. Intestinal and pancreatic secretions and bile have high quantities of HCO_3^-, therefore conditions like diarrhea, removal of pancreatic or intestinal secretions or bile by tube drainage or fistula leads to loss of HCO_3^- and metabolic acidosis. Hyperchloremic acidosis may also result from ureterosigmoidostomy due to presence in the colon of an anion exchange pump that absorbs luminal Cl^- (of urinary origin) and exchanges it for HCO_3^-, and due to colonic absorption of NH_4^+ (of urinary origin) that releases H^+ when metabolized in the liver. Cholestyramine also causes metabolic acidosis by acting as anion exchange resins, where colonic luminal HCO_3^- is absorbed in exchange for Cl^- released by the resin.

LABORATORY EVALUATION

Evaluation in patients with metabolic acidosis and suspected RTA requires consecutive tests as detailed below and in **Table 1**.

Plasma anion gap All types of RTA are associated with hyperchloremic normal anion gap metabolic acidosis. Hence, assessment of the anion gap helps distinction between RTA and diarrhea that causes hyperchloremic acidosis with normal anion

Table 1 Important tests in the evaluation of patients with metabolic acidosis

Evaluation	Calculation; normal level	Interpretation in metabolic acidosis
Plasma anion gap	$[Na^+] - \{[Cl^-] + [HCO_3^-]\}$ *Normal:* 8–16 mEq/L	*Increased:* Diabetic ketoacidosis; lactic acidosis; inborn errors; poisoning; uremia *Normal:* Renal tubular acidosis (RTA); diarrhea; impaired renal function
Urine anion gap	Urinary $[Na^+] + [K^+] - [Cl^-]$ *Normal:* Positive	*Positive:* Diarrhea; extrarenal losses of HCO_3^- *Negative:* RTA
Urine pH	$- \log_{10}[H^+]$ *Normal:* 4.6–8.0	*< 5.3:* Normal response; proximal RTA; type 4 RTA *> 5.3:* Distal RTA (classic, incomplete); hyperkalemic distal RTA
Fractional excretion of bicarbonate (%)	$\dfrac{\text{Urine } HCO_3^- \times \text{Plasma creatinine}}{\text{Plasma } HCO_3^- \times \text{Urine creatinine}} \times 100$ *Normal:* < 5%	*< 5%:* Normal, distal RTA, type 4 RTA *5–15%:* Distal RTA *> 15%:* Proximal RTA
Fractional excretion of phosphate (%)	$\dfrac{\text{Urine } PO_4^{3-} \times \text{Plasma creatinine}}{\text{Plasma } PO_4^{3-} \times \text{Urine creatinine}} \times 100$ *Normal:* < 5–15%	*< 5–12%:* Normal, distal RTA, type 4 RTA *> 15%:* Proximal RTA
Transtubular potassium gradient	$\dfrac{\text{Urine } K^+ \times \text{Plasma osmolality}}{\text{Plasma } K^+ \times \text{Urine osmolality}}$ *Normal:* 6–12	*In hyperkalemia:* > 10: normal response *< 8:* Type 4 RTA

gap, from diabetic ketoacidosis, lactic acidosis and other causes of increased anion gap acidosis **(Table 1)**. While advanced renal failure with GFR below 15 mL/min is associated with metabolic acidosis and elevated anion gap, normal anion gap acidosis is often noted in patients with estimated GFR 20–50 mL/min.

Urine anion gap (urine net charge) The difference between the sum of urinary Na^+ and K^+ and urinary Cl^- indirectly estimates NH_4^+ excretion in patients with hyperchloremic metabolic acidosis. Since the sum of charges on urinary cations and anions is equal, and the difference between urinary unmeasured anions (sulfates, phosphates, organic anions) and cations (calcium, magnesium) is fairly constant at about 80 mEq/L, hence:
$Na^+ + K^+ + NH_4^+ + \text{Unmeasured cations} = Cl^- + \text{Unmeasured anions}$;
or
$NH_4^+ = [\text{Unmeasured anions} - \text{Unmeasured cations}] -$
$$[Na^+ + K^+ - Cl^-];$$
or
$NH_4^+ = 80 - \text{Urinary anion gap}$; *or* Urinary anion gap $= 80 - NH_4^+$.

Under normal circumstances, the urinary anion gap is positive due to the presence of dissolved anions. Patients with systemic acidosis from extrarenal HCO_3^- losses (e.g., diarrhea) have intact mechanisms of renal acidification resulting in enhanced NH_4^+ synthesis and excretion along with Cl^- ions, causing the urinary anion gap to become negative. A positive urinary anion gap indicates inappropriately low renal NH_4^+ excretion, as in patients with all forms of RTA. The test enables distinction between patients with RTA, in whom urinary NH_4^+ excretion is low, from extrarenal HCO_3^- losses (e.g., diarrhea) where its excretion is high.

Urine pH Urine pH measures the concentration of free H^+ and assesses the integrity of distal H^+ secretion. In presence of systemic acidosis, urine pH is normally less than 5.3; pH greater than 5.3 suggests defective distal urinary acidification. Urine pH values are less than 5.3 in subjects with systemic acidosis due to type 4 RTA and those with proximal RTA when filtered load of HCO_3^- is low (plasma $HCO_3^- < 15$ mEq/L). The pH should be measured electrometrically on fresh voided specimen, since dipsticks are unreliable and urine left standing might get contaminated with urea splitting organisms, resulting in high urine pH.

Induced systemic acidosis If systemic acidosis is absent, an oral load of ammonium chloride is given, followed by the measurement of urine pH and NH_4^+ excretion. A decline in plasma CO_2 content by 3–5 mEq/L is accompanied by fall in urine pH to less than 5.3.

Bicarbonate loading test Sodium bicarbonate ($NaHCO_3$) is given orally or as an intravenous (IV) infusion, while measuring urine pH in timed samples collected under mineral oil. Loading is continued till consecutive samples show urine pH greater than 7.5 and plasma HCO_3^- greater than 22–24 mEq/mL. The fractional excretion of HCO_3^- ($FEHCO_3^-$) and urine to blood (U-B) PCO_2 gradient are measured to enable characterization of RTA.

Urine to blood CO_2 gradient Loading with $NaHCO_3$ makes luminal HCO_3^- available to combine with H^+ secreted by distal tubules. Carbonic acid dehydrates to form CO_2 that is trapped in the tubular lumen. In presence of urine pH greater than 7.5 and normal plasma HCO_3^-, the urine PCO_2 should exceed 70 mm Hg and the U-B PCO_2 gradient is greater than 20 mm Hg if the distal acidification is intact. Patients with decreased rates of tubular H^+ secretion (classical distal RTA) show urine PCO_2 less than 50 mm Hg and U-B PCO_2 less than 10 mm Hg. Patients with other forms of RTA show normal urinary PCO_2 values. The U-B PCO_2 gradient is considered a sensitive indicator of distal acidification.

Fractional excretion of bicarbonate Proximal tubules normally reabsorb almost all filtered HCO_3^-. Following alkalization to normalize serum HCO_3^- (> 22 mEq/L), $FEHCO_3^-$ provides a useful assessment of proximal tubular handling of HCO_3^-: while values greater than 15% indicate proximal RTA, levels are in the normal range (< 5%) in distal and type 4 RTA.

The interpretation of the above tests is summarized in **Tables 1 and 2**. Based on initial evaluation, the following additional tests may be useful.

Proximal Renal Tubular Acidosis

The diagnosis of proximal RTA requires evaluation of other proximal tubular functions. These include assessment of (1) phosphate excretion, (2) aminoaciduria, (3) glucosuria, (4) low molecular weight proteinuria (e.g., β_2-microglobulin), (5) hypercalciuria and (6) rickets. Patients should be screened for cystinosis, galactosemia and Wilson's disease.

Tests for phosphate handling Low levels of plasma phosphate and increased fractional excretion of phosphate indicate proximal tubular phosphate wasting, noted in Fanconi syndrome. The fractional excretion of phosphate is determined on a timed (6 hours, 12 hours or 24 hours) urine specimen and is normally less than 5–12%. The tubular reabsorption of phosphate (TRP, 100 – fractional excretion) is 88–95%. Since TRP varies according to

Table 2 Investigations to differentiate types of renal tubular acidosis (RTA)

	Proximal RTA	Distal RTA		Type 4 RTA
		Classic	Hyperkalemic	
Plasma K^+	Normal/low	Normal/low	High	High
Urine pH	< 5.3	> 5.3	> 5.3	< 5.3
Urine anion gap	Positive	Positive	Positive	Positive
Urine NH_4^+	Low	Low	Low	Low
Fractional HCO_3^- excretion	> 10–15%	< 5%	< 5%	> 5–10%
U-B PCO_2 mm Hg	> 20	< 20	$</>$ 20	> 20
Urine Ca^{2+}	Normal	High	High	Normal/low
Other tubular defects	Often present	Absent	Absent	Absent
Nephrocalcinosis	Absent	Present	Present	Absent
Bone disease	Common	Often present	Uncommon	Absent

Abbreviation: U-B PCO_2, urine to blood PCO_2 gradient

the plasma phosphate and GFR, tubular maximum for phosphate, corrected for GFR is a sensitive tool of phosphate reabsorption, the normal value being 2.8–4.4 mg/dL.

Distal Renal Tubular Acidosis

An ultrasonography is performed to detect nephrocalcinosis and/or calculi. Urinary excretion of calcium and citrate is measured to detect hypercalciuria and hypocitraturia. All patients should undergo hearing evaluation; evaluation for lupus, osteopetrosis, Sjögren syndrome and chronic hepatitis is done in patients presenting at an older age.

Fludrocortisone furosemide test Administration of furosemide (2 mg/kg, with or without fludrocortisone 0.02 mg/kg) unmasks the defect in patients with distal RTA by increasing distal Na^+ delivery and reabsorption, leading to luminal electronegativity in the cortical collecting tubule. In healthy individuals, this results in urine pH less than 5.3 and increase in K^+ excretion. In patients with hypokalemic distal RTA, the urine pH does not fall but the K^+ excretion increases, indicating intact function of principal cells. Patients with hyperkalemic distal RTA have a primary defect in cortical Na^+ reabsorption and do not show increase in H^+ or K^+ excretion since luminal electronegativity is not enhanced. Patients with type 4 RTA and proximal RTA show normal response.

Type 4 Renal Tubular Acidosis

Work-up includes evaluation for obstructive uropathy or tubulointerstitial disease. Measurement of plasma renin activity and aldosterone levels are useful. The transtubular potassium gradient (TTKG) is useful in diagnosing type 4 RTA and in conjunction with mineralocorticoid challenge helps distinguish deficiency from aldosterone resistance.

Transtubular potassium gradient This test is an index of K^+ gradient in the distal tubular lumen and interstitium and provides an accurate assessment of aldosterone effect on late distal and cortical collecting tubules in patients with hyperkalemia and normal renal function. Normal individuals have TTKG between 6 and 12; in presence of hyperkalemia, TTKG should rise to greater than 10 **(Table 2)**. Inappropriately low TTKG (< 8) suggests hypoaldosteronism or tubular resistance to aldosterone;

subsequent rise in TTKG to greater than 7 upon administering fludrocortisone suggests hypoaldosteronism.

TREATMENT

Proximal Renal Tubular Acidosis

Correction of acidosis may require administration of 5–20 mEq/kg/day of alkali, often as $NaHCO_3$ (5–8 mEq/kg/day). Since large amounts of alkali are lost in urine as HCO_3^-, restriction of dietary sodium and administration of hydrochlorothiazide (1.5–2 mg/kg/day) help by causing contraction of extracellular fluid volume that increases HCO_3^- reabsorption. Since thiazides enhance K^+ excretion, part of the alkali should be given as potassium citrate. Correction of acidosis results in improved growth velocity.

Patients with Fanconi syndrome require management of the underlying condition and replacement of losses of Na^+, K^+, HCO_3^- and phosphate. Adequate fluid intake is advised, particularly during infancy and illnesses. Rickets responds to supplements of phosphate (50–100 mg/kg/day), vitamin D and correction of acidosis.

Distal Renal Tubular Acidosis

Acidosis is corrected by administering alkali solution at 2–3 mEq/kg/day titrated to blood HCO_3^- levels. The requirement of HCO_3^- is high initially but decreases later. Hypokalemia should be treated before correcting the acidosis. While correction of acidosis decreases tendency for hypokalemia, patients may require prolonged potassium supplements. The response to therapy is significant but may be delayed, particularly in older children. While early treatment leads to reduction of hypercalciuria and increase in citrate excretion, use of thiazides may be required in persistent hypercalciuria.

Type 4 Renal Tubular Acidosis

Hyperkalemia requires potassium restriction regardless of etiology. Therapy is directed towards specific cause. Patients with aldosterone deficiency benefit from fludrocortisone supplementation. Therapy with thiazides corrects the abnormalities in PHA type 2. Patients with recessive form of PHA type 1 require large amounts of salt supplements.

SPECIFIC CONDITIONS ASSOCIATED WITH RENAL TUBULAR ACIDOSIS

Dent Disease

This rare X-linked disorder is characterized by low molecular weight proteinuria, hypercalciuria, nephrolithiasis and/or nephrocalcinosis and progressive renal failure. Most patients are detected when evaluated for renal calculi in adolescence. Findings may include features of proximal tubule dysfunction, such as aminoaciduria, glucosuria, hyperphosphaturia, kaliuresis and uricosuria, consistent with Fanconi syndrome; however, metabolic acidosis is uncommon. The underlying defect is a loss of function mutation in the gene encoding the voltage-gated chloride channel, *CLCN5*, or less commonly, that for phosphatidylinositol-4,5-bisphosphate-5-phosphatase, *OCRL1*.

Lowe Syndrome

The oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked recessive condition characterized by anomalies of the eyes, nervous system and kidneys. Abnormalities include bilateral congenital cataract, strabismus, infantile onset glaucoma and keloids. Neurological involvement is manifest as hypotonia, hyporeflexia since birth, severe psychomotor retardation, behavioral abnormalities (temper tantrums, stereotypes, aggressiveness, obsessive compulsive behavior) and seizures. Fanconi syndrome is noted during early infancy. Facial dysmorphism includes frontal bossing, deep-set eyes, chubby cheeks and fair complexion.

The disease is caused by mutations in the gene *OCRL1* encoding the Golgi complex enzyme phosphatidylinositol-4,5-bisphosphate-5-phosphatase. Accumulation of the enzyme substrate, phosphatidylinositol bisphosphate alters protein trafficking, actin cytoskeleton polymerization and endocytosis. Mothers carrying the pathogenic mutation show punctate white-gray radial opacities in lens on slit lamp examination. Treatment is symptomatic, including cataract extraction, glaucoma control, physical and speech therapy, drugs to modify behavior and appropriate therapy for acidosis and bone disease. Most patients succumb to respiratory illness, seizures or renal failure by adulthood.

Cystinosis

This autosomal recessive condition is characterized by deposition of cystine crystals in the cornea, conjunctiva, bone marrow, leukocytes, lymph nodes and other organs. The disease is caused by mutations in the *CTNS* gene encoding for the protein, cystinosin that transports cystine from lysosomes to cytosol. Patients present in late infancy or early childhood with polyuria, polydipsia, failure to thrive and refractory rickets; photophobia is delayed but progressive. Renal injury, manifesting as Fanconi syndrome, progresses to end-stage renal disease by the end of first decade. Rarely, the disease is benign, with cystine deposits in cornea, bone marrow and leukocytes sparing the kidneys, or present as an intermediate form with incomplete Fanconi syndrome appearing during adolescence.

Diagnosis is suggested by detection of corneal cystine crystals on slit lamp examination; confirmation requires high levels of cystine in leukocytes. Management is for Fanconi syndrome and long-term administration of cysteamine that removes cystine from lysosomes. Cysteamine eyedrops, administered frequently, reduce corneal crystals. Long-term outcome is complicated by diabetes mellitus and hypothyroidism, in addition to end-stage renal disease.

Mitochondrial Cytopathies

Mitochondrial cytopathies are diverse disorders with abnormalities in the mitochondrial DNA causing dysfunction in various organs.

Impaired respiratory chain activity causes accumulation of reduced nicotinamide adenine dinucleotide (NADH), promoting conversion of acetoacetic acid into 3-hydroxybutyrate in mitochondria and pyruvate into lactate in cytosol. Patients present with neurological symptoms (apnea, lethargy, developmental delay, stroke like episodes, seizures, myoclonus, polyneuropathy, myopathy or hypotonia), but cardiac (cardiomyopathy, arrhythmias, heart block), endocrine and hematological (sideroblastic anemia, neutropenia, thrombocytopenia) involvement is common. Renal features include proximal tubular defects including Fanconi syndrome, tubulointerstitial nephritis, cystic renal disease and glomerulopathies. The tubulopathy is frequently associated with Pearson and Kearns-Sayre syndromes.

Diagnosis is suggested by presence of tubulopathy, proteinuria or hematuria along with neurological symptoms and high serum or cerebrospinal fluid lactate, with increased ratio of lactate to pyruvate. Investigations include magnetic resonance spectroscopy (elevated cerebral lactate), gas chromatography/mass spectrometry (elevated urinary organic acids) and genetic studies. Renal biopsy shows chronic tubulointerstitial changes with damaged proximal tubules; electron microscopy shows proliferation of abnormal mitochondria. Most inherited conditions are fatal. Apart from HCO_3^- and phosphate supplements, oral CoQ10 supplementation may be useful.

IN A NUTSHELL

1. Renal tubular acidosis is characterized either by failure of HCO_3^- reabsorption or lack of H^+ secretion by the distal tubule.
2. Clinical features include failure to thrive, muscle weakness, polyuria and rickets; nephrocalcinosis is common in distal RTA.
3. Key investigations that distinguish proximal from distal RTA include estimation of urine pH, $FEHCO_3^-$, and U-B PCO_2 gradient.
4. Additional investigations that assist in distinguishing proximal from distal RTA include estimation of urine calcium, screening for glucosuria, aminoaciduria and phosphate excretion, and ultrasonography for renal stones and nephrocalcinosis.
5. Principles of treatment include correction of acidosis and dyselectrolytemia.
6. Patients with Fanconi syndrome require additional supplements of phosphate and electrolytes; all patients should also be screened for an underlying cause.

MORE ON THIS TOPIC

Bagga A, Bajpai A, Menon S. Approach to renal tubular disorders. Indian J Pediatr. 2005;72:771-6.

Bagga A, Sinha A. Evaluation of renal tubular acidosis. Indian J Pediatr. 2007;74:679-86.

Emma F, Bertini E, Salviati L, Montini G. Renal involvement in mitochondrial cytopathies. Pediatr Nephrol. 2012;27:539-50.

Escobar L, Mejia N, Gil H, Santos F. Distal renal tubular acidosis: a hereditary disease with an inadequate urinary H^+ excretion. Nefrologia. 2013;33:289-96.

Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. Nephrol Dial Transplant. 2012;27:4273-87.

Haque SK, Batlle D. Genetic causes and mechanisms of distal renal tubular acidosis. Nephrol Dial Transplant. 2012;27:3691-704.

Rodríguez-Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. 2002;13:2160-70.

Chapter 41.15
Tubular Disorders
Kamran Afzal

HYPOKALEMIA AND METABOLIC ALKALOSIS

Hypokalemia, defined as serum potassium (K^+) concentration below 3.5 mEq/L, could result from dietary insufficiency, increased renal or extrarenal losses of potassium or its abnormal distribution. Most patients with metabolic alkalosis also have hypokalemia. Extrarenal and renal causes of hypokalemia with metabolic alkalosis are given in **Box 1**. In this section, renal tubular disorders that are associated with hypokalemia, metabolic alkalosis and normal blood pressure are discussed. These include chiefly Bartter syndrome and Gitelman syndrome, better described as *Bartter-like syndrome*. The presence of renal potassium loss and alkalosis with hypertension suggests conditions associated with mineralocorticoid excess.

Adult patients with Gitelman syndrome are more common than Bartter syndrome but during childhood the prevalence is similar. The disorders are uncommon in childhood but are possibly under diagnosed.

Bartter Syndrome

First reported by Bartter and colleagues in 1962, this group of inherited autosomal recessive renal tubular disorders is characterized by hypokalemia, metabolic alkalosis, hyper-reninemia and hyperaldosteronism with normal blood pressure, and increased urinary sodium, chloride, and potassium wasting. Based on age at presentation, the disease is categorized into neonatal Bartter and classic Bartter syndrome. Neonatal Bartter syndrome can be suspected before birth or can be diagnosed

BOX 1   Causes of hypokalemia with metabolic alkalosis

Extrarenal wasting of potassium
(urinary K^+ < 20 mEq/L) with metabolic alkalosis/normal pH
• Laxative abuse, villous adenoma, congenital chloride losing diarrhea, congenital pyloric stenosis
 	
Renal potassium wasting
(urinary K^+ > 20 mEq/L)
• With normal blood pressure
   – *Increased renin and aldosterone*: Bartter syndrome, Gitelman syndrome, magnesium losing tubulopathy, calcium losing tubulopathy, diuretic abuse
• With hypertension
   – *Decreased renin and aldosterone*: Pseudohyperaldosteronism (Liddle syndrome), syndrome of apparent mineralocorticoid excess
   – *Decreased renin and increased aldosterone (primary hyperaldosteronism)*: Aldosterone-producing adenoma, adrenocortical carcinoma
   – *Increased renin and increased aldosterone (secondary hyperaldosteronism)*: Renal artery stenosis, renin-secreting tumor.

immediately after birth. In the classic form, symptoms begin in neonates or in infants aged 2 years or younger.

Pathophysiology

There are four types of Bartter syndrome based on whether the underlying molecular defect involves the sodium-potassium-chloride cotransporter (NKCC2), ROMK potassium channel or the chloride channel, ClCK **(Figs 1A and B)**. Type 1, 2 and 4 are neonatal forms while type 3 is classic Bartter syndrome **(Table 1)**.

Clinical Features

Infants with neonatal Bartter syndrome are generally born preterm and have marked intrauterine polyuria with resultant
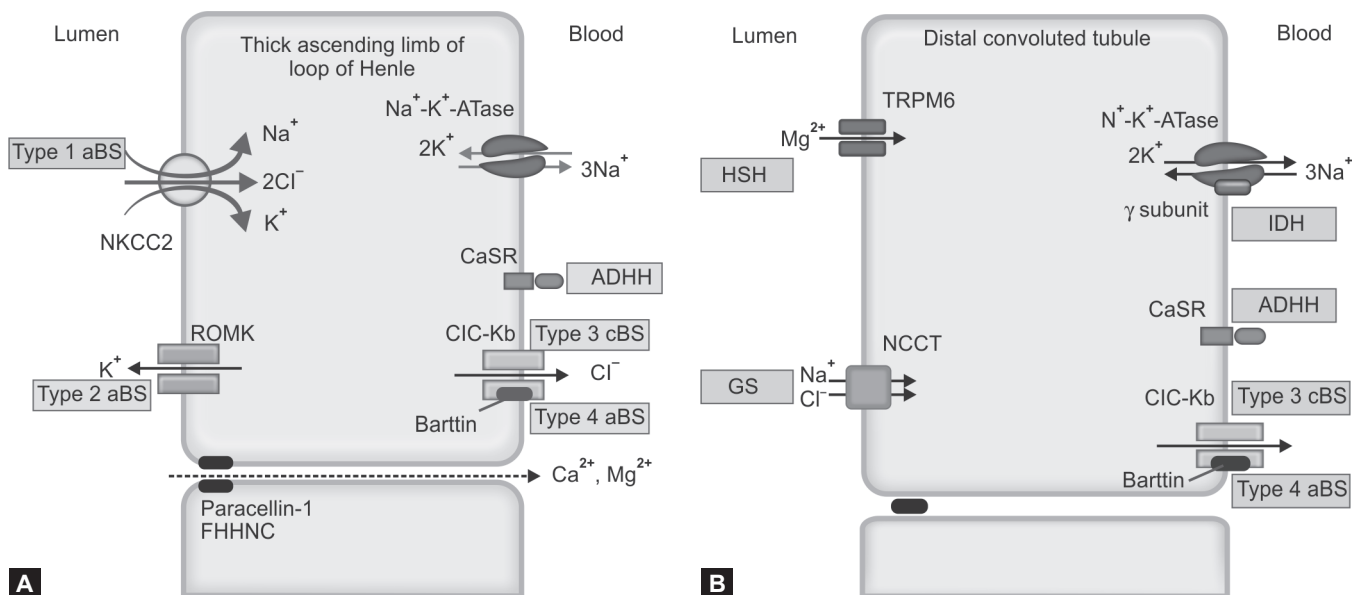
Figures 1A and B Electrolyte channels and associated tubular disorders of the
(A) thick ascending limb of loop of Henle and (B) distal convoluted tubule

Abbreviations: NKCC2, Na-K-2CL cotransporter; NCCT, NaCl cotransporter; ClCKb, chloride channel; Paracellin-1, claudin 16; CaSR, calcium-sensing receptor; aBS, antenatal Bartter syndrome; cBS, classic Bartter syndrome; GS, Gitelman syndrome; ADHH, Autosomal dominant hyperparathyroidism; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; HSH, hypomagnesemia with secondary hypocalcemia; IDH, isolated dominant hypomagnesemia.

Table 1 Tubular disorders associated with hypokalemia and metabolic alkalosis

Disorder	Chromosome, locus	Gene product; location	Inheritance	Features
Bartter syndrome (BS)				
• Type 1 (antenatal BS)	*SLC12A1*; 15q15-q21.1	Furosemide-sensitive sodium potassium cotransporter-2 (NKCC2); TALH	AR	Antenatal polyhydramnios, prematurity, hypokalemia, metabolic alkalosis, nephrocalcinosis, failure to thrive
• Type 2 (antenatal BS)	*KCNJ1*; 11q24	ROMK potassium channel; TALH, cortical collecting duct	AR	Same as type 1
• Type 3 (classic BS)	*CLCNKB*; 1p36	Chloride channel, CLCKb; TALH, DCT	AR	Hypokalemia, metabolic alkalosis, failure to thrive, hypercalciuria, no nephrocalcinosis
• Type 4 (antenatal BS with sensorineural deafness)	*BSND*; 1p31	Barttin, a chloride channel; TALH, DCT	AR	Same as type 1, sensorineural deafness
Gitelman syndrome	*SLC12A3*; 16q13	Thiazide-sensitive sodium chloride cotransporter (NCCT); DCT	AR	Hypokalemia, metabolic alkalosis, failure to thrive, hypocalciuria, hypomagnesemia, chondrocalcinosis
Autosomal dominant hypocalcemia with hypercalciuria (ADHH)	*CaSR* activating mutations; 3q13	CaSR; TALH	AD	Childhood onset hypokalemia, alkalosis, failure to thrive, hypercalciuria, low PTH, hypomagnesemia, nephrocalcinosis

Abbreviations: TALH, thick ascending limb of loop of Henle; DCT, distal convoluted tubule; AR, autosomal recessive; AD, autosomal dominant; CaSR, calcium-sensing receptor.

polyhydramnios. Polyuria, up to 12–50 mL/kg/hour, continues postnatally and often results in severe dehydration. Polydipsia, salt-craving, and growth failure are common. Marked hypercalciuria with nephrocalcinosis is consistent with the neonatal form and rare in the classic type. Chronic hypokalemia has been associated with metabolic perturbations and nephropathy.

Laboratory Diagnosis
Sodium and chloride wasting and volume contraction result in release of renin, hyperaldosteronism, kaliuresis, severe hypokalemia (serum potassium 1.5–2.0 mEq/L), hypochloremic metabolic alkalosis and hyperprostaglandism with increase in urinary excretion of prostaglandin E_2. Hyponatremia and hyperuricemia are often associated. Urinary chloride concentration typically exceeds 25–35 mEq/L. Hypercalciuria and nephrocalcinosis are more common in the neonatal type and often persist despite therapy.

Differential Diagnoses
Nonrenal causes of chloride loss such as vomiting and cystic fibrosis can be excluded by the presence of low urinary chloride, less than 10 mEq/L. Patients with type 2 Bartter syndrome may be confused with primary pseudohypoaldosteronism (PHA) type 1 because of similar clinical features in the first weeks of life. Hypomagnesemia is uncommon in Bartter syndrome and necessitates exclusion of Gitelman syndrome.

Management
Treatment primarily aims to correct hypokalemia and volume deficit. Supplementation of potassium as KCl 1–3 mEq/kg/day is done. Additionally potassium-sparing diuretics (spironolactone 10–15 mg/kg/day or triamterene 10 mg/kg/day) may be used. The most effective drugs, however, are prostaglandin synthetase inhibitors, chiefly indomethacin (2–4 mg/kg/day). Careful watch for adverse effects of indomethacin such as nausea, vomiting, abdominal pain, peptic ulcer, and renal or hepatic toxicity is needed.

Outcome
Some patients may show clinical improvement but recurrences may occur. Long-term prognosis is guarded with progression to chronic renal failure in adulthood.

Gitelman Syndrome
This autosomal recessive disorder results from defective functioning of thiazide-sensitive sodium chloride (NaCl) cotransporter NCCT of distal convoluted tubule due to inactivating mutations in its gene *SLC12A3*, locus 16q13 **(Figs 1A and B)**.

Pathophysiology
The syndrome is characterized by hypokalemia, hypocalciuria, metabolic alkalosis, and hypomagnesemia due to defective functioning of NCCT in distal tubules.

Clinical Features
Unlike Bartter syndrome, Gitelman syndrome is generally a milder disease with presentation in late childhood to early adulthood. However, half the patients complain of salt-craving, episodes of muscular cramps, abdominal pain, fatigue and sometimes tetany. Growth retardation and polyuria are mild. Chloride wasting is always less than in Bartter syndrome and urinary excretion of prostaglandin E_2 is normal.

Treatment
Treatment is with oral supplementation of magnesium and potassium chloride.

Outcome
Magnesium supplements are needed lifelong, but overall long-term outcome is excellent with preserved renal functions.

HYPERKALEMIA AND METABOLIC ACIDOSIS
Hyperkalemia (serum potassium more than 6 mEq/L) may result from increased intake, or transcellular shifts but is mostly

caused by decreased renal potassium excretion. Decreased renal potassium excretion could result from reasons extrinsic to the kidney, e.g., mineralocorticoid deficiency, or those intrinsic to kidney such as renal failure and renal tubular disorders that limit potassium excretion. Since potassium excretion increases with decline in glomerular filtration rate (GFR), the effect of aldosterone on the distal and collecting tubules is assessed using transtubular potassium gradient (TTKG), given by the formula:

$$TTKG = \frac{Urine\ potassium \times Serum\ osmolality}{Serum\ potassium \times Urine\ osmolality}$$

Normal values range from 4.1 to 10.5 (4.9 to 15.5 for infants). Values below this range indicate mineralocorticoid deficiency or unresponsiveness. Renal tubular acidosis (RTA) type 1 and 2 are associated with hypokalemia and are discussed in the previous chapter. In this section, we discuss type 4 RTA, disorders of mineralocorticoid associated with hyperkalemia and acidosis.

Mineralocorticoid Deficiency

Type 4 renal tubular acidosis results from inadequate production of or reduced distal tubular responsiveness to aldosterone **(Box 2)**. Absence of aldosterone-mediated sodium reabsorption results in hyperkalemia, which subsequently suppresses renal ammonia production, resulting in a reduction of net acid excretion. This results in a hyperkalemic, hyperchloremic acidosis that may render the urine pH acidic (< 5.5).

Mineralocorticoid (aldosterone) deficiency RTA may result from disorders of the adrenal gland [Addison disease, congenital adrenal hyperplasia (CAH), primary hypoaldosteronism]. These disorders have elevated plasma renin, urinary sodium wasting and preserved renal functions.

Hyporeninemic hypoaldosteronism may result from renal diseases associated with tubulointerstitial damage or destruction of the juxtaglomerular apparatus wherein the renal function may be affected.

Distal tubular receptor insensitivity to aldosterone (PHA) is a rare cause of type 4 RTA associated with elevated plasma renin and aldosterone levels, normal renal function, and salt wasting.

BOX 2 Causes of mineralocorticoid (aldosterone) deficiency or resistance

- Hyper-reninemic hypoaldosteronism (primary adrenal insufficiency or Addison disease)
  - Defects of aldosterone biosynthesis (congenital adrenal hyperplasia): Deficiency of 21-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, aldosterone synthase deficiency
  - Adrenal tuberculosis; necrosis
- Hyporeninemic hypoaldosteronism [pseudohypoaldosteronism (PHA)]
  - Primary PHA
    - *Type 1:* Autosomal dominant renal form, autosomal recessive mutisystem form
    - *Type 2* (Gordon syndrome)
  - Secondary PHA
    - Renal diseases with aldosterone deficiency
    - Obstructive uropathy, interstitial nephritis, sickle cell nephropathy, nephrocalcinosis
- Aldosterone resistance
  - Post-transplantation
  - *Drugs:* Amiloride, spironolactone, ACE inhibitors, heparin, NSAIDs, calcineurin inhibitors.

Clinical Features

Patients with type 4 RTA present with features of hyperkalemia and metabolic acidosis. Nephrocalcinosis and urolithiasis are absent in this disorder. The most common acquired cause of type 4 RTA in children is obstructive uropathy. Inherited causes, particularly CAH secondary to 21-hydroxylase deficiency and the autosomal recessive form of PHA type 1, should be considered in the differential diagnoses in infants presenting with salt loss, hypotension and hyperkalemia. Receptor insensitivity or autosomal dominant PHA type 1 is due to mutation in the collecting tubule mineralocorticoid receptor is a less severe disease and improves with age. Autosomal recessive forms of PHA type 1 are due to defective epithelial sodium channels (ENaC) and present in infancy with life-threatening hyperkalemia, salt wasting, metabolic acidosis, and hypotension. Gordon syndrome (PHA type 2), an autosomal dominant condition, results from mutation in the WNK1 and *WNK4* genes (lysine deficient protein kinase genes). Affected patients present with hypertension, hyperkalemia, hyporeninemia, hypoaldosteronism, metabolic acidosis, and volume expansion that is often responsive to thiazide diuretics.

Differential Diagnosis

Before the diagnosis of RTA is considered, other causes of systemic acidosis, such as diarrhea, inborn errors of metabolism, ingestion, lactic acidosis, diabetes mellitus, and renal failure, should be excluded. The biochemical features of proximal and distal RTA include low serum bicarbonate and potassium levels in association with hyperchloremia. In mineralocorticoid deficiency RTA, systemic acidosis is associated with hyperkalemia. The anion gap in all forms of RTA is usually normal.

Treatment

The goal of treatment is to identify the underlying etiology to guide therapy. Often the cause is not directly treatable, so supplemental alkali therapy is given to correct acidosis and improve growth and bone mineralization. Drug-induced type 4 RTA is treated with discontinuation of the offending medication. In cases due to PHA from obstructive uropathy, adequate urinary tract drainage with normal saline infusion and sodium bicarbonate therapy will correct acidosis. Aldosterone deficiency should be treated with mineralocorticoid (fludrocortisone) replacement. Children with type 4 RTA due to PHA type 1 require salt supplementation and potassium restriction.

Pseudohypoaldosteronism type 2 is treated with thiazide diuretics and salt restriction. Patients with other causes of hyperkalemia and type 4 RTA may respond to symptomatic management of hyperkalemia with dietary restriction. A loop diuretic and/or a cation exchange resin may be required in some cases.

NEPHROGENIC DIABETES INSIPIDUS

Diabetes insipidus (DI) is a condition associated with the passage of large volumes, of dilute urine that results from either too little or no antidiuretic hormone [arginine vasopressin (AVP)] release [central diabetes insipidus (CDI)] or from an inability to respond to AVP in the kidney [nephrogenic diabetes insipidus (NDI)]. In children, NDI is more common than CDI, and is most often acquired. Congenital forms of NDI are more severe and difficult to

treat. X-linked NDI accounts for 90% of all the congenital forms of NDI. Acquired NDI is due to different forms of kidney disease or metabolic derangements **(Table 2)**.

Central diabetes insipidus can be idiopathic, hereditary or caused by intracranial injury or disease. A decrease in urine volume and an increase in urine osmolality occur with the administration of exogenous AVP.

Nephrogenic diabetes insipidus is mostly an X-linked recessive disorder with loss of function or dysfunction mutation of the V2 receptor gene (*AVPR2*; locus Xq28) responsible for the inability to concentrate urine in up to 90% cases despite the presence of AVP in the circulation. Autosomal recessive or autosomal dominant presentations usually represent a defect in aquaporin-2 (*AQP2* gene, locus 12q13)—the water channel normally generated when AVP binds to its receptor on the renal tubule epithelium.

Clinical Features

With any form of DI, the signs and symptoms include: polyuria (urine volume > 6 mL/kg/hour in neonates; > 4 mL/kg/hour or > 2 L/m^2 in children), and polydipsia. The large urine volumes occur despite osmotic, or volume stimuli for AVP release. In the X-linked NDI, the affected males typically present in the newborn period with poor feeding and growth, irritability, recurrent vomiting, and constipation. Severe polyuria and polydipsia manifest within a few months. Older children present with enuresis, constipation, and recurrent episodes of dehydration, hypernatremia, fever. Unlike CDI, mental retardation is seen with variable severity in children with NDI attributed to intracranial calcification. Poor growth, learning and behavioral difficulties, delayed bladder control and a flow uropathy (megaureter and megacystis) may be associated.

Laboratory Diagnosis

Once polyuria is established by measurement of 24 hours urine volume, exclude other causes of solute diuresis by measuring

Table 2 Causes of diabetes insipidus in children

Central diabetes insipidus	Nephrogenic diabetes insipidus
Congenital	*Congenital*
• *Familial:* Autosomal dominant or recessive	• *X-linked recessive:* Xq28 encoding *AVPR2* receptor
• DIDMOAD syndrome—*WFS1* gene defect (chromosome 4p16)	• *Autosomal recessive:* Chromosome 12q13 encoding aquaporin-2 receptor (*AQP2*)
• *Congenital anatomic defects:* Holoprosencephaly, agenesis of corpus callosum, septo-optic dysplasia	• Autosomal dominant
Acquired	*Acquired*
• Trauma, surgery, hemorrhage, thrombosis	• *Renal disease:* Obstruction, renal hypoplasia, dysplasia, polycystic kidney disease, nephronophthisis, medullary cystic disease, urate nephropathy
• *Infection:* Meningitis, encephalitis, *Cryptococcus*	
• *Primary or metastatic tumors:* Lymphoma, leukemia, germinoma, pinealoma, craniopharyngioma	• *Metabolic:* Hypercalcemia, hypokalemia
• *Granulomatous disease:* Tuberculosis, sarcoidosis	• *Drugs:* Lithium, amphotericin B, aminoglycosides, diuretics, ifosfamide, others
• *Drugs:* Phenytoin, carbamazepine, valproic acid, adrenergic drugs	
Idiopathic 10–25%	

serum and urine glucose, calcium and potassium. The first morning urine specific gravity more than 1.010 virtually excludes the possibility of DI. Urine osmolality of more than 800 mOsm/kg with a serum osmolality of less than 270 mOsm/kg also rules out the diagnosis of DI, whereas dilute urine with an osmolality of less than 300 mOsm/kg, and a serum osmolality of more than 300 mOsm/kg effectively establishes the diagnosis. DI, both central and nephrogenic can be partial or complete. Water deprivation test coupled with vasopressin test **(Box 3)** helps to establish the diagnosis and differentiate CDI from NDI **(Table 3)**. Magnetic resonance imaging (MRI) of pituitary is an important tool for assessment of etiology of CDI.

Treatment

Desmopressin [1-deamino-8-D-arginine vasopressin (DDAVP)] is the current drug of choice for long-term therapy of CDI. The recommended dose of DDAVP is 100–1,200 μg/day in three divided doses orally; 2–40 μg once or twice a day intranasally; and, 0.1–1 μg parenterally.

Nephrogenic diabetes insipidus will not respond to exogenous AVP. Reduction in the intake of osmols by salt restriction to

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BOX 3 Water deprivation and vasopressin test

Water deprivation test
- Fasting begins after dinner, bladder is emptied at 8 am, weight recorded, and blood and urine specimens are collected for osmolality
- Subsequently measure body weight and urine volume hourly; assess for signs of dehydration. Collect urine and blood samples
- The test is discontinued if
  – Duration of water deprivation exceeds 7 hours (4 hours in infants)
  – Weight loss ≥ 5% of body weight
  – Three consecutive hourly urine osmolality values are within 10% of each other
  – At any time plasma osmolality > 300 mOsmol/kg or urine osmolality > 800 mOsmol/kg (> 500 mOsmol/kg for infants)

Vasopressin test
- Vasopressin test is performed to distinguish nephrogenic diabetes insipidus from central diabetes insipidus. Desamino-8-D-arginine vasopressin (DDAVP), desmopressin is administered nasally (5–10 μg in neonates and infants, 20 μg in children) or by a subcutaneous injection 0.5 μg/m^2. Hourly urine collection for osmolality is done over the next 3–4 hours. Following administration of DDAVP, patients with NDI fail to show a rise of urine osmolality, which remains below 200–300 mOsm/kg. Those with CDI and primary polydipsia concentrate urine to varying degrees.

Table 3 Interpretation of water deprivation and vasopressin test

Urine osmolality after water deprivation (mOsmol/kg)	% change in urine osmolality after DDAVP	Interpretation
> 800	Minimal or no change	Normal
< 300	> 50%	CDI
300–800	10–50%	Partial CDI
300–800	< 10%	Partial NDI or primary polydipsia
< 300	< 10%	NDI

Abbreviations: CDI, central diabetes insipidus; NDI, nephrogenic diabetes insipidus.

50–100 mmol/day of NaCl and the reduction in protein intake to 1–1.5 g/kg/day of high-quality protein have been recommended. Adequate water intake and access to water is a must. Diuretic use, specifically hydrochlorothiazide 2–4 mg/kg/24 hours divided two times/day or chlorothiazide 25–50 mg/kg/24 hours divided two times/day along with amiloride 0.2–0.4 mg/kg/day (reduces potassium wasting associated with thiazide diuretics) also reduces polyuria. Indomethacin 0.7–1.5 mg/kg/day reduces GFR, thereby decreases total water loss, but long-term use may be associated with adverse effects.

MAGNESIUM HANDLING BY KIDNEYS

Normal plasma magnesium concentration is kept within narrow limits, 1.7–2.1 mg/dL. Hypomagnesemia (< 1.7 mg/dL) can be caused by low dietary intake, poor gastrointestinal absorption, or excessive urinary excretion. It is often associated with hypocalcemia and hypokalemia. A fractional excretion of magnesium of more than 4% in a child with normal renal function is indicative of renal magnesium wasting. Several inherited tubular disorders are responsible for urinary magnesium wasting **(Table 4)**. Gitelman syndrome has been discussed in the previous section. On a normal diet, the fractional excretion of magnesium is 3–5%, and the healthy kidney has the ability to decrease this to less than 1% in the setting of extrarenal causes of hypomagnesemia. Major renal resorption of magnesium occurs in the proximal tubules (15–20%) and the loop of Henle (65–75%) through paracellular pathways **(Figs 1A and B)**.

Hypomagnesemia

The classic sign of severe hypomagnesemia (< 1.2 mg/dL) is hypocalcemia resulting in increased neuromuscular excitability manifesting as tetany, carpopedal spasm, tremors, muscle cramps or seizures. The hypocalcemia is secondary to parathyroid failure and peripheral parathyroid hormone (PTH) resistance as a result of magnesium deficiency. In addition, cardiac arrhythmias including atrial and ventricular tachycardia, prolonged QT interval may be noted. Hypomagnesemia is frequently associated with other abnormalities including hypocalcemia and hypokalemia. Degree of symptoms may not always correlate with serum levels as magnesium is predominantly intracellular and serum levels do not accurately reflect total body stores.

Differential Diagnosis

The differential diagnosis of hypomagnesemia includes both hereditary forms **(Table 4)** and acquired causes **(Box 4)**.

BOX 4 Causes of acquired hypomagnesemia

Inadequate intake
- Deficient diet, parenteral nutrition without magnesium

Defective gastrointestinal absorption
- Malabsorption (celiac disease, inflammatory bowel disease), chronic diarrhea

Increased urinary losses
- *Diuresis:* Postobstructive, diuretic phase of renal transplantation or acute tubular necrosis
- States of hyperparathyroidism or hyperaldosteronism
- *Drugs:* Diuretics (e.g., loop or thiazide diuretics), antibiotics (e.g., aminoglycosides, amphotericin B, pentamidine), antineoplastic agents (cisplatin), immunosuppressive drugs (e.g., cyclosporine)

Intracellular shift
- Repiratory alkalosis, insulin therapy, hungry bone syndrome postparathyroidectomy, refeeding syndrome of malnutrition.

Table 4 Syndromes associated with magnesium wasting

Disorder	Gene, locus	Gene product; location	Inheritance	Features
Gitelman syndrome	*SLC12A3*, 16q12.3	Thiazide-sensitive NaCl cotransporter (NCCT); DCT	AR	Hypokalemia, metabolic alkalosis, hypocalciuria
Hypomagnesemia with secondary hypocalcemia (HSH)	*TRPM6*, 9q22	*TRPM6;* DCT	AR	Hypocalcemia (secondary to parathyroid failure), calcinosis in heart, kidney, cerebral arteries (seizures, choreoathetosis, speech disturbance)
Isolated dominant familial hypomagnesemia (IDH)	*FXYD2*, 11q23	γ-subunit of Na-K-ATPase; DCT	AD	Variable symptoms, tetany, seizures, hypocalciuria, no hypokalemia or nephrocalcinosis
Isolated recessive familial hypomagnesemia	Not known	Not known	AR	Variable
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)	*CLDN16*, 3q28	Claudin-16, TALH	AR	Nephrocalcinosis, sensorineural deafness, seizure, progressive renal failure
Familial hypomagnesemia, hypercalciuria, nephrocalcinosis, ocular involvement	*CLDN19*, 1p34	Claudin-19, TALH	AR	Hypocalcemic tetany, nephrocalcinosis, sensorineural deafness, myopia magna, retinitis pigmentosa, nystagmus
Autosomal dominant hypocalcemia with hypercalciuria (ADHH)	Calcium-sensing receptor (*CaSR*) gene 3q13	CaSR activating mutation; TAHL, DCT	AD	Hypocalcemia, hypercalciuria, and polyuria

Abbreviations: TALH, thick ascending limb of loop of Henle; DCT, distal convoluted tubule; AR, autosomal recessive; AD, autosomal dominant.

Laboratory Diagnosis

Evaluation of hypomagnesemia should start with a careful history and physical examination, with particular attention to dietary intake and use of offending medications. Laboratory evaluation should include serum magnesium, phosphorus, calcium, and measures of glomerular and tubular functions. Urinary magnesium quantification is helpful to determine renal versus extrarenal magnesium losses. Fractional excretion more than 4% generally indicates renal magnesium wasting.

Treatment

Oral magnesium replacement is associated with diarrhea due to its cathartic action. In neonates and children, the initial treatment usually consists of 25–50 mg magnesium sulfate (0.1–0.2 mmol magnesium) per kilogram body weight slowly given intravenously (over 20 min) (up to a maximum of 2 g). This dose can be repeated every 6–8 hours or can be followed by a continuous infusion of 100–200 mg magnesium sulfate (0.4–0.8 mmol magnesium) per kilogram body weight given over 24 hours. In the presence of hypocalcemia, this regimen can be continued for 3–5 days. Careful cardiac monitoring in these patients is advised and special caution is required in cases of renal insufficiency.

MORE ON THIS TOPIC

Bagga A, Sinha A. Evaluation of renal tubular acidosis. Indian J Pediatr. 2007;74:679-86.

Cole DE, Quamme GA. Inherited disorders of renal magnesium handling. J Am Soc Nephrol. 2000;11:1937-47.

Konrad M, Weber S. Recent advances in molecular genetics of hereditary magnesium-losing disorders. J Am Soc Nephrol. 2003;14:249-60.

Mishra G, Chandrashekhar SR. Management of diabetes insipidus in children. Indian J Endocrinol Metab. 2011;15 Suppl 3:S180-7.

Rodríguez-Soriano J. New insights into the pathogenesis of renal tubular acidosis—from functional to molecular studies. Pediatr Nephrol. 2000;14:1121-36.

Rodríguez-Soriano J. Tubular disorders of electrolyte regulation. In: Avner ED, Harmon WE, Niaudet P. Pediatric Nephrology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2004. pp. 729-56.

Seyberth HW, Schlingmann KP. Bartter- and Gitelman-like syndromes: salt-losing tubulopathies with loop or DCT defects. Pediatr Nephrol. 2011;26: 1789-802.

IN A NUTSHELL

1. Bartter syndrome and Gitelman syndrome are rare tubular disorders of electrolyte regulation that result in variable degrees of hypokalemia, metabolic alkalosis, hyponatremia and urinary chloride wasting.

2. Clinical features of Bartter syndrome include polyuria, polydipsia, salt-craving, muscle cramps and failure to thrive.

3. The different types of Bartter syndrome vary by age of onset, severity of symptoms, associated electrolyte abnormalities (including hypomagnesemia) and magnitude of urinary calcium wasting.

4. Gitelman syndrome is a milder disease that is distinguished by the presence of hypomagnesemia and hypocalciuria.

5. Treatment consists of supplementation with KCl (and $MgCl_2$ for Gitelman syndrome). Indomethacin is used in children with Bartter syndrome.

6. Type 4 RTA results in normal anion gap metabolic acidosis and hyperkalemia.

7. Blood pressure may be low, normal or high. Plasma renin and aldosterone levels may be increased or decreased.

8. Obstructive uropathy is the most common acquired cause. Among hereditary forms, CAH secondary to 21-hyroxylase deficiency and autosomal recessive PHA type 1 are important.

9. Mineralocorticoid supplementation as fludrocortisone is useful in patients with CAH and Addison disease. Patients with recessive form of PHA type 1 need lifelong salt supplements. Therapy with thiazides corrects the abnormalities noted in patients with PHA type 2.

10. Nephrogenic diabetes insipidus is more common among children than CDI; acquired causes are more common than congenital.

11. Of the congenital nephrogenic DI, 90% are X-linked recessive type.

12. Water deprivation test and vasopressin test help to establish the diagnosis.

13. Central diabetes insipidus responds to replacement with exogenous AVP, as DDAVP. NDI is resistant to DDAVP and is managed with fluid replacement, diuretics (thiazide and amiloride) and indomethacin.

Chapter 41.16
Renal Calculi
Indira Agarwal

Urinary stone disease is rare in children but when present, is associated with metabolic abnormalities that can lead to recurrent stone disease and significant morbidity. In children its presentation, diagnosis and management may be unique as it may be secondary to a systemic disease, renal disease or infection.

EPIDEMIOLOGY

In India, upper and lower urinary tract stones occur frequently but the incidence shows a wide regional variation. The prevalence is high in Satpura part of Maharashtra, parts of Rajasthan and Punjab which are regarded as the stone belt. In recent years, the epidemiology of urinary stone disease has been changing with improving social conditions, particularly in urban areas of more affluent developing countries.

TYPES OF STONES

Calcium oxalate and calcium phosphate account for 75% of all stones due to major consumption of cereals like millet (high in calcium and phosphate), lack of animal protein and high consumption of oxalate-rich vegetables. Struvite (ammonium magnesium phosphate) accounts for 20% of cases, uric acid 4% and cystine stones (cystine or cystine and calcium) about 1% cases.

PATHOGENESIS

Low intake of fluids causes supersaturation of stone forming salts. Food intake may also predispose to stone formation, e.g., increased dairy intake predisposes to hypercalciuria and animal protein increases uric acid production. Vegetarian diet is rich in oxalate, predisposing to its increased urinary excretion. Hypocitraturia and hypomagnesemia cause increased calcium oxalate supersaturation. High urinary concentrations of calcium, oxalate, uric acid and cystine cause solute excess either due to increased renal excretion or low urine volume. This leads to solute supersaturation and precipitation and formation of crystals that may aggregate into stone. Inhibitors of stone formation include citrate, magnesium and pyrophosphate.

Hypercalciuria

This is the most common metabolic abnormality associated with pediatric renal calculi. It is defined as urinary calcium excretion of greater than 4 mg/kg/day in a child more than 2 years old while ingesting a routine diet. If difficult to obtain 24 hours sample, a spot or total calcium creatinine ratio may be measured. These children may present with hematuria, dysuria, urinary frequency or nephrocalcinosis.

Patients with idiopathic hypercalciuria represent a complex interaction between genetic and environmental factors. Idiopathic hypercalciuria is a monogenic defect secondary to increased intestinal absorption or reduced renal tubular reabsorption of calcium. Secondary causes of hypercalciuria include Dent's disease, Bartter syndrome, Wilson disease, glycogen storage disease type 1a, distal renal tubular acidosis and familial hypomagnesemia. Urinary calcium excretion may be increased in patients with dehydration, immobilization with increased bone resorption, medications such as loop diuretics and glucocorticoids, and large doses of vitamin D. Conditions associated with hypercalcemia, e.g., hyperparathyroidism and sarcoidosis also result in hypercalciuria.

Hyperoxaluria

While urinary oxalate greater than 50 mg/1.73 m²/24 hours is considered significant, normative values vary by age and assay method. Primary hyperoxaluria types I and II are rare autosomal disorders characterized by enhanced conversion of glyoxylate to poorly soluble oxalate resulting in increased serum oxalate and hyperoxaluria. Patients present in early childhood with nephrocalcinosis and/or renal stones and progressive kidney disease. Children with fat malabsorption may have enhanced enteric absorption of oxalate since excess fatty acids bind calcium resulting in less calcium being available to combine with oxalate and prevent its absorption. Children with inflammatory bowel disease, extensive bowel resection, pancreatitis and cystic fibrosis are also at risk for hyperoxaluria and nephrolithiasis. Excessive ingestion of ethylene glycol and ascorbic acid results in increased serum oxalate and hyperoxaluria.

Hyperuricosuria

Increased urinary excretion of uric acid can result from enhanced renal excretion alone or its increased production. Idiopathic hyperuricosuria results from a defect in renal tubular uric acid excretion and is often seen in conjunction with hypercalciuria. Overproduction of uric acid occurs in tumor lysis syndrome, lymphoproliferative and myeloproliferative disorders, rare genetic disorders such as Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency) and glycogen storage diseases. A high dietary intake of purines is associated with uric acid nephrolithiasis.

Cystinuria

Cystinuria, an autosomal recessive disorder, is characterized by excessive excretion of the dibasic amino acids—cystine, arginine, lysine and ornithine. It is caused by mutations and/or genomic rearrangements in two genes *SLC3A1* and *SLC7A9*. The colorless flat, hexagonal cystine crystals found in the urinary sediment are diagnostic, but identified only in 20–25% of cases.

Hypocitraturia

Citrate is an inhibitor of calcium oxalate and calcium phosphate crystallization. Hypocitraturia is reported in 10% of children with renal calculi. Children with chronic metabolic acidosis have an increased risk of nephrolithiasis because enhanced proximal renal tubular citrate reabsorption decreases citrate excretion, leading to stone formation.

Infection

Urinary tract infection may be the primary cause of a stone or occurs concomitantly with an underlying metabolic or structural abnormality in 20–25% cases. Functional or anatomic obstruction of the urinary tract predisposes children to stasis and infection, which promote stone formation. Bacteria producing the enzyme urease are strongly associated with pediatric nephrolithiasis and include *Proteus*, *Providencia*, *Klebsiella*, *Pseudomonas* and enterococci. Urease breaks down urea to form ammonium and bicarbonate, which creates a favorable biochemical milieu for the formation of struvite stones (magnesium ammonium phosphate). These stones, which can contain carbonate apatite, tend to branch, enlarge and fill renal calyces, producing a *staghorn* appearance.

Xanthogranulomatous pyelonephritis is a rare, severe chronic infection of the kidney that leads to renal parenchymal destruction and chronic inflammation characterized by lipid-laden macrophages resulting in a nonfunctioning or poorly functioning kidney. Nephrectomy or partial nephrectomy is required to treat these patients.

Structural Abnormalities

Congenital abnormalities that cause urinary stasis are associated with nephrolithiasis. These include medullary sponge disease, autosomal dominant polycystic kidney disease, ureteropelvic junction obstruction, horseshoe kidney, bladder exstrophy, augmentation of the bladder and neurogenic bladder.

CLINICAL FEATURES

Most children with nephrolithiasis present with flank or abdominal pain. Young children may be asymptomatic, stones being detected when abdominal imaging is performed for other purposes. Ureteral stones are painful, since they cause ureteral obstruction; dysuria and urgency may suggest urinary tract infection. Hematuria is the sole symptom or observed with abdominal pain in 30–55%.

DIAGNOSIS

Plain abdominal radiograph detects radiopaque stones (e.g., calcium, struvite and cystine stones) but will miss radiolucent stones (uric acid), small stones and those overlying bony structures. Further, urinary obstruction cannot be detected. Ultrasonography is the most commonly used technique to detect calculi. This modality can detect radiolucent uric acid stones and presence of urinary obstruction. However, the modality is investigator-dependent and is limited in its ability to uncover small stones (< 5 mm), papillary or calyceal stones and ureteral stones. Noncontrast helical computed tomography (CT) is the most sensitive modality to detect renal or ureteral stones. CT also provides detailed information enabling detection of obstruction and/or structural anomalies.

Laboratory Evaluation

Suggested evaluation for etiology of renal calculi is listed in **Box 1**. Examination of the urine sediment is useful if crystals are present and may be identified by their characteristic shape. Cystine crystals are flat and hexagonal, calcium oxalate crystals are pyramid or envelope-shaped, magnesium ammonium phosphate crystals are like coffin lids and uric acid are diamond-shaped. Knowledge of reference values for urinary metabolites is vital while interpreting their excretion **(Tables 1 and 2)**.

MANAGEMENT

Medical Management

Both nonsteroidal anti-inflammatory drugs and opioids are useful in controlling pain associated with nephrolithiasis. Fluid intake should be increased by 150% to reduce the risk of supersaturation and potential for crystallization. *Chemolysis* is the method of maintaining an alkaline urinary pH for acidic stones like uric acid, oxalate and cystine, and an acidic pH for struvite stones, using oral potassium citrate and acid phosphate preparations, respectively. Dietary restriction of sodium is useful in restricting

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BOX 1 Initial screening for patients with renal stones

- Urine microscopy, culture and sensitivity
- Blood urea, creatinine, sodium, potassium, chloride, calcium, magnesium, bicarbonate, phosphate, uric acid, alkaline phosphatase
- Ultrasound of kidneys, ureter and bladder
- Plain abdominal radiograph
- Stone analysis (if passed or removed surgically)
- Spot urine for ratios of calcium, cystine, oxalate and uric acid to creatinine
- 24 hours urine collection for calcium, sodium, potassium, magnesium, citrate, oxalate, cystine, uric acid and xanthine.

Table 1 Reference ranges for solute excretion in 24 hours urine specimens

Solute	Reference range
Calcium	< 4 mg (0.1 mmol)/kg
Sodium	< 3 mEq (3 mmol)/kg
Potassium	> 3 mEq (3 mmol)/kg
Magnesium	> 88 mg (44 mmol)/1.73 m^2
Citrate	> 180 mg [94 μmol/g (8.84 mmol)] creatinine
Oxalate	< 52 mg (593 mmol)/1.73 m^2; < 2 mg (23 mmol)/kg
Cystine	< 60 mg (0.5 mmol)/1.73 m^2
Uric acid	< 815 mg (4.9 mmol)/1.73 m^2; < 35 mg (0.21 mmol)/kg
Xanthine	30–90 μg (20–60 μmol)

Table 2 Reference range for spot urine samples

Urine constituent	Age	Value, mg/mg creatinine
Calcium: Creatinine	0–6 months	< 0.8
	7–12 months	< 0.6
	≥ 2 years	< 0.21
Oxalate: Creatinine	< 1 year	0.15–0.26

hypercalciuria. Intake of diet rich in calcium and low on oxalate reduces hyperoxaluria. Since urinary tract infections may be associated with nephrolithiasis, urine culture should be obtained if the child is symptomatic and appropriate antibiotic therapy initiated.

Stone Passage

Most stones less than 5 mm in diameter pass spontaneously, even in small children. Hydration increases urinary flow and facilitates stone passage. While alpha-blockers have been used to facilitate stone passage in distal ureteral stones, their routine use is not recommended. Stone analysis provides the stone composition that can guide further evaluation and suggest measures to prevent recurrences. Ultrasonography is used to monitor stone passage, and repeated X-rays or CT scans avoided.

Urological Intervention

The decision to intervene surgically depends on the location, size and composition of stone and the presence of accompanying obstruction and infection. Intervention may be considered if there are signs of infection, complete or partial obstruction, renal insufficiency, or stone greater than 5 mm in diameter. Chief indications are the following:

Unremitting severe pain Pain persisting despite adequate analgesia is usually caused by stone obstructing the ureterovesical or pelviureteric junction. Pain is relieved with a temporizing ureteral stent and subsequent stone removal.

Impaired differential renal function Urinary obstruction causes renal parenchymal injury and decrease in renal function. Intervention in patients with mild renal insufficiency demonstrates improvement in renal function due to relief of obstruction and subsequent recovery of injured renal tissue. The goal of management is thus to minimize renal injury, balancing the risk of the urologic procedure versus harm from continued obstruction.

Struvite calculi These calculi usually require removal in order to eradicate the infection with urease-producing bacteria (e.g., *Proteus* or *Klebsiella*), which is a risk factor for recurrent stone

Table 3 Choice of procedure

Location/Type	Size	Choice of procedure
Lower pole calculi	Any size	Extracorporeal shock wave lithotripsy (ESWL), or ureteroscopy
Radiopaque, in renal pelvis	< 1 cm	ESWL
In renal pelvis	1–2 cm	Percutaneous nephrolithotomy (PCNL), or ESWL
In renal pelvis	> 2 cm	PCNL, ureteroscopy, ESWL
Pelviureteric junction obstruction		PCNL
Calyceal diverticulum		PCNL
Cystine and calcium oxalate monohydrate stones		PCNL, ureteroscopy
Struvite, uric acid or calcium oxalate dihydrate		ESWL

Abbreviations: ESWL, extracorporeal shock wave lithotripsy; PCNL, percutaneous nephrolithotomy.

formation and predisposes to sepsis. Struvite stones are usually too large to pass spontaneously as they tend to branch and fill the renal calyces.

Procedures

Table 3 highlights the choice of procedure according to location/type of calculi.

Extracorporeal shock wave lithotripsy Extracorporeal shock wave lithotripsy (ESWL) employs high energy shock waves produced by an electrical discharge and is effective and safe in children. For stones less than 2 cm in diameter, the resulting fragments are usually passed without difficulty, but may take several months to clear. If the stone is greater than 2 cm in diameter, stents are placed to reduce the risk of obstruction.

Percutaneous nephrolithotomy (*PCNL*) Following percutaneous access to the collecting system, the tract is dilated with a balloon dilator, and the stone is either extracted with a grasping forceps or fragmented with *laser*, ultrasonic, pneumatic or hydraulic lithotripsy probe. PCNL and ESWL can be performed in conjunction.

Ureteroscopy Ureteroscopy is used in pediatric patients as first-line therapy in the management of ureteral calculi as well as following failure of ESWL. Once the stone is visualized, it is extracted with grasping forceps or basket, or fragmented with *laser*, ultrasonic or electrohydraulic lithotripsy. Patients with upper tract stones (stones in the poles of the pelvis) may require multiple sessions and/or ureteral stenting.

IN A NUTSHELL

1. Calcium oxalate and calcium phosphate account for 75% of all stones; struvite (ammonium magnesium phosphate) accounts for 20% of cases, uric acid 4% and cystine stones (cystine or cystine and calcium) about 1% cases.
2. Predisposing factors include structural abnormalities, infection, hypercalciuria, hyperuricosuria, hypocitraturia, and hyperoxaluria.
3. Most children with nephrolithiasis present with abdominal pain and/or hematuria.
4. Ultrasonography is the most commonly used technique to detect calculi.
5. Surgical intervention is considered if there are signs of infection, complete or partial obstruction, renal insufficiency, or stone greater than 5 mm in diameter.

MORE ON THIS TOPIC

Dogan HS, Tekgul S. Minimally invasive surgical approaches to kidney stones in children. Curr Urol Rep. 2012;13:298-306.

Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28:1923-42.

Gnessin E, Chertin L, Chertin B. Current management of paediatric urolithiasis. Pediatr Surg Int. 2012;28:659-65.

Monico CG, Milliner DS. Genetic determinants of urolithiasis. Nat Rev Nephrol. 2011;8:151-62.

Razzak M. Paediatric urology: kids with stones—data on causes and treatment safety. Nat Rev Urol. 2013;10:618.

Chapter 41.17
Refractory Rickets
Abhijeet Saha

Calcium and phosphate are required for normal bone growth and mineralization. Impairment in the process of mineralization presents as rickets and/or osteomalacia among children and osteomalacia alone in adults. Failure or delay of mineralization at the unfused growth plates in children results in widening and splaying of the growth plate, with widened wrists, double malleoli, prominent costochondral junctions and bowing of legs. Defect in mineralization of already developed osteoid results in deformed long bones, termed as osteomalacia.

Vitamin D deficiency is the chief cause of nutritional rickets world over, including areas with adequate sun exposure. Whole body clothing, living predominantly indoors and industrial pollution are the chief reasons for limited sun exposure. Other factors include malabsorption and severe calcium deficiency. Therapy for nutritional rickets comprises of administration of vitamin D at a dose of 100,000–600,000 IU (2.5–15 mg) over 1–5 days or 60,000 IU (1.5 mg) every week for 6–8 weeks. Subsequently, 400 IU of vitamin D per day is administered along with calcium at 30–75 mg/kg/day in divided doses for 2–4 weeks. Once levels of parathormone (PTH) and 25(OH)D$_3$ are normal and vitamin D supplementation reduced to 400 IU/day, calcium supplementation is not necessary. Increase in serum phosphate is the first biochemical change seen around 1–2 weeks after high-dose therapy. Radiographic changes of rickets are best sought in rapidly growing bones, such as the distal ulna and metaphyses of knees. Radiologic healing begins within 1 week; complete resolution may take months and a repeat X-ray should be performed after 4 weeks of therapy.

Vitamin D refractory rickets is a clinical condition where child fails to show evidence of radiological healing and correction of biochemical abnormalities despite adequate therapy. Most experts would administer a second dose of vitamin D at 4 weeks if healing of rickets does not occur after first dose, and make a diagnosis of refractory rickets if no healing is observed even after second dose, i.e., after 8 weeks of initiating therapy. Predominant causes of vitamin D refractory rickets include abnormal vitamin D metabolism and defective renal tubular phosphate handling **(Box 1)**.

BOX 1 Etiology of vitamin D refractory rickets

Calcipenic rickets (increased parathormone)
- Vitamin D-dependent rickets type I (1α-hydroxylase deficiency)
- Vitamin D-dependent rickets type II
- Chronic kidney disease

Phosphopenic rickets (normal parathormone)
- Renal phosphate leak with increased fibroblast growth factor 23
  - *Hypophosphatemic rickets:* X-linked, autosomal recessive, autosomal dominant
  - Tumor-induced osteomalacia
  - McCune-Albright syndrome
  - Linear nevus sebaceous syndrome
- Renal phosphate leak with hypercalciuria
  - Distal renal tubular acidosis
  - Hereditary hypophosphatemic rickets with hypercalciuria
  - Dent's disease, Lowe syndrome
- Fanconi syndrome
  - Primary
  - *Secondary:* Cystinosis, galactosemia

ETIOLOGY

Calcipenic rickets is characterized by increased levels of PTH, resulting in internalization of tubular phosphate transporters and impaired phosphate reabsorption. Low plasma phosphate with normal PTH is feature of phosphopenic rickets. This might arise from increased production of fibroblast growth factor 23 (FGF23), a phosphaturic hormone, or from renal tubular disorders resulting in renal phosphate wasting. Renal tubular acidosis (RTA), hypophosphatemic rickets and vitamin D-dependent rickets (VDDR) are common causes of nonazotemic refractory rickets in Indian children.

PATHOPHYSIOLOGY

In the epidermis, 7-dehydrocholesterol (provitamin D) is converted to previtamin D by ultraviolet B waves from the sun. Previtamin D isomerizes to cholecalciferol (vitamin D$_3$) and passes to dermal capillaries where it binds to vitamin D-binding protein. Vitamin D$_3$ is also present in fatty fish (salmon, herring, cod, mackerel, sardine), shiitake mushrooms, liver, cod liver oil and egg yolk. Ergocalciferol (vitamin D$_2$) is consumed as plants and yeast. Vitamin D$_2$ and D$_3$ ingested from food incorporate into micelles in gut enterocytes and are processed into chylomicrons. Vitamin D$_3$ is more potent than vitamin D$_2$ because of a greater affinity for binding proteins; when taken in equivalent doses it causes a greater increase in serum calcidiol, 25(OH)D$_3$. Transportation of vitamins D$_2$ and D$_3$ to the liver is followed by conversion to 25(OH)D$_3$ by the cytochrome *CYP2R1*. Because calcidiol has little feedback effect on its own synthesis, its serum levels approximate body stores of vitamin D. Following filtration, 25(OH)D$_3$ is reabsorbed in proximal tubules, entering mitochondria where it is 1-hydroxylated to the biologically active hormone 1,25(OH)$_2$ vitamin D$_3$ [1,25(OH)$_2$D$_3$] (calcitriol). Cytochrome P450 mono-oxygenase 25(OH) vitamin D-1-α-hydroxylase, encoded by *CYP27B1*, regulates 1,25(OH)$_2$D$_3$ synthesis. It is stimulated by PTH, PTH-related protein, calcitonin, hypocalcemia, hypophosphatemia, growth hormone, prolactin, 24,25(OH)$_2$D and insulin-like growth factor 1. It is suppressed directly by high levels of calcium and phosphorus, inhibitory autofeedback, FGF23, and indirectly by suppression of synthesis of PTH. The biological half-life of calcitriol is 4 hours. Within minutes of binding to its nuclear receptor, calcitriol promotes intestinal absorption of calcium and opening of voltage-gated calcium channels in osteoblasts. Calcitriol stimulates growth plate chondrocytes, increases generation of osteoblasts and type l collagen formation, and suppresses osteoclastic resorption; calcitriol also inhibits transcription of PTH in the parathyroid glands.

Vitamin D-dependent rickets type I, also known as pseudovitamin D deficiency rickets, is an autosomal recessive disease associated with diminished or absent synthesis of 1,25(OH)$_2$D$_3$ due to deficiency of the 25-hydroxyvitamin D$_3$ 1α-hydroxylase enzyme in the kidney. Numerous mutations in the *CYP27A1* gene that encodes 25(OH)D$_3$ 1α-hydroxylase in the kidney have been described. Mutations in the vitamin D receptor gene are the cause of VDDR type II; patients show end-organ resistance to vitamin D.

Tubular reabsorption of phosphate is carried out by sodium-coupled phosphate (NaPi) cotransporters localized at the apical membrane of tubular cells. The cotransporters NaPi-IIa and NaPi-IIc are expressed in the proximal brush border membranes. NaPi-IIa transporter is the key mediator of proximal phosphate reabsorption. Dietary phosphate is absorbed through the small intestine, predominantly in the jejunum. To maintain balance, the amount of phosphate absorbed in the intestine is similar to

the amount excreted in the urine. This balance is maintained and closely regulated by the coordinated actions of hormones, including osteocyte-derived FGF23, PTH and $1,25(OH)_2D_3$ **(Fig. 1)**.

Phosphate wasting in hypophosphatemic rickets is associated with elevated FGF23. FGF23 causes phosphaturia by downregulating NaPi-IIa and NaPi-IIc in proximal renal tubules; it also inhibits 25(OH) vitamin D 1α-hydroxylase, promotes 25(OH) D 24-hydroxylase and inhibits PTH secretion. The X-linked form of hypophosphatemic rickets (XLHR) is mediated by loss-of-function mutations in *PHEX*, an endopeptidase encoded by a gene on X chromosome. The autosomal dominant form is associated with heterozygous mutations that impair degradation of FGF23; the recessive type involves loss of function mutations in dentin matrix protein 1 or ecto/nucleotide pyrophosphatase/phosphodiesterase 1 that inhibit production of FGF23. Rarely, mesenchymal tumors secrete excess amounts of FGF23 leading to tumor-induced osteomalacia.

CLINICAL FEATURES

Rickets initially manifests at the distal forearm, knee and costochondral junctions as these are the sites of rapid bone growth and mineralization. Hypoplasia of the dental enamel is common in calcipenic rickets. Patients with VDDR type I present in early infancy with muscle weakness, rickets and hypocalcemic seizures. Physical examination may show positive Trousseau and Chvostek signs. VDDR type II is characterized clinically by an early onset of rickets, poor linear growth, alopecia, epidermal cysts and loss of teeth.

Features of hypophosphatemic rickets include bowing of legs, muscle weakness, bone pain and short stature. Deformity of legs is noted with the onset of walking. Defective dentin formation results in dental abscesses and loss of teeth. Clinical findings are limited to legs and findings like rachitic rosary and wrist widening are usually absent. XLHR may be associated with hearing impairment that is apparent in adulthood.
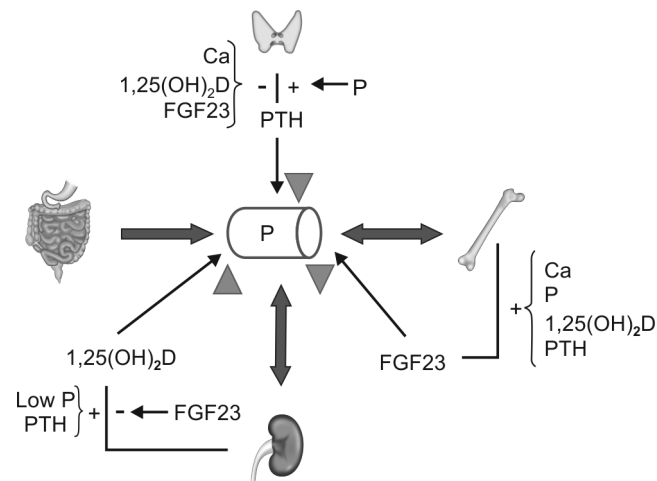
Figure 1 Phosphorus homeostasis. Serum concentrations of phosphate (P) depend on intestinal absorption, renal elimination and release from bone. These processes are regulated by serum parathormone (PTH), fibroblast growth factor 23 (FGF23) produced by osteocytes and $1,25(OH)_2D_3$. PTH and FGF23 reduce levels of phosphate, while $1,25(OH)_2D_3$ increases these levels (green arrowheads). Secretion of these hormones is in turn regulated by reciprocal interplay and by feedback of serum levels of calcium (Ca) and P

Features of RTA include growth failure, polyuria, polydipsia and preference of savory food. Patients with proximal RTA have either isolated bicarbonaturia or Fanconi syndrome (glucosuria, aminoaciduria, phosphaturia, uricosuria and bicarbonaturia) secondary to cystinosis, galactosemia, tyrosinemia, Wilson disease or Lowe syndrome. Manifestations of distal RTA are growth impairment, polyuria, nephrocalcinosis, nephrolithiasis and symptoms due to hypokalemia. Distal RTA in children is usually primary; rare cases are secondary to systemic lupus erythematosus or Sjögren syndrome. Children with chronic kidney disease have growth retardation, bone deformities and anemia.

DIFFERENTIAL DIAGNOSIS

Some systemic diseases have features similar to rickets. Hypophosphatasia is characterized by disordered mineralization of bones secondary to deficient tissue nonspecific alkaline phosphatase activity, resulting from loss of function mutations in the liver/bone/kidney alkaline phosphatase gene. Six clinical forms are recognized that vary in severity and age at onset. Deformities noted in the childhood variant include enlarged joints, dolichocephaly, short stature and waddling gait. Signs of intracranial hypertension, failure to thrive, fractures and bone pain are common. Radiographs show widespread demineralization and rachitic changes at ends of metaphysis. Low serum levels of alkaline phosphatase and increased urinary phosphoethanolamine support the diagnosis.

Fluorosis is endemic in many Asian countries including China and India. High levels of fluorine are reported in drinking water from Seemandhra, Telangana, Gujarat and Rajasthan. Bony deformities and radiological features mimic rickets. Dental caries is common. Serum levels of alkaline phosphatase and PTH are raised. Urinary levels of fluoride are high.

APPROACH TO DIAGNOSIS

Radiological signs of rickets include splaying, fraying, cupping and demineralization of the distal radial and ulnar metaphyses along with widening of the physis. Investigations include serum levels of calcium, phosphate, PTH, $25(OH)D_3$, $1,25(OH)_2D_3$, renal functions tests and venous blood gas. Phosphaturia should be assessed by calculation of tubular reabsorption of phosphate and maximal tubular reabsorption of phosphorus per glomerular filtration rate (TmP/GFR). Urine is analyzed for calcium, phosphate and creatinine on timed and spot specimens. The presence of sugar, albumin and aminoaciduria suggests Fanconi syndrome; aminoaciduria is also seen in patients with VDDR type I. Patients with metabolic acidosis need evaluation to diagnose and characterize RTA (*See* Chapter 41.14).

Vitamin D deficiency is characterized by low levels of phosphorus and 25(OH) vitamin D_3; levels of PTH and alkaline phosphatase are raised. Since secondary hyperparathyroidism may cause phosphaturia, the TmP/GFR is estimated after vitamin D levels are corrected. **Table 1** shows important alterations in various forms of rickets. An algorithm for evaluation is depicted in **Flow chart 1**.

MANAGEMENT

Patients with hypophosphatemic rickets need oral phosphorus supplementation at 40–60 mg/kg/day in the form of neutral phosphate solution or tablets or Joulie's solution. The use of multiple daily doses is advised as serum phosphate levels return to low baseline values within a few hours of phosphate supplementation.

Table 1 Laboratory diagnosis of rickets

	Calcium	Phosphorus	Alkaline phosphatase	Parathormone	25(OH) vitamin D	1,25(OH)$_2$ vitamin D	Urinary calcium	TmP/GFR
Vitamin D deficiency	N or ↓	↓	↑	↑	↓	N or ↑	↓ or N	
Calcium deficiency	↓	↓	↑	↑	N	↑	↓	
VDDR type I	↓	↓ or N	↑↑	↑	N	↓↓	↓	
VDDR type II	↓	↓ or N	↑↑	↑	N	↑↑	↓	
Hypophosphatemic rickets								
X-linked	N	↓	↑	N	N	N or ↓	↓	↓
Autosomal dominant	N	↓	↑	N	N	N	N	↓
With hypercalciuria	N	↓↓	↑	N or ↓	N	↑	↑	↓
Fanconi syndrome	N	↓	N or ↑	N or ↑	N	N or ↓	N or ↑	↓
Chronic kidney disease	↓	↑	↑	↑	↓	↓	↓	

Abbreviations: TmP/GFR, ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate; VDDR, vitamin D-dependent rickets.

Flow chart 1 Diagnostic approach to refractory rickets
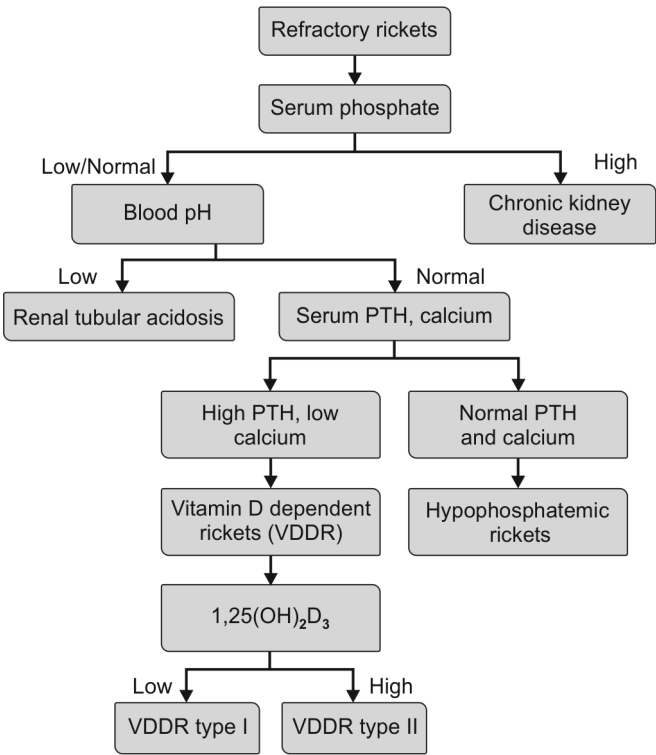
In addition, an active form of vitamin D (1–2 μg/day alfacalcidol or 0.5–1 μg/day calcitriol) is necessary to counter the 1,25(OH)$_2$D$_3$ deficiency. The dose of vitamin D analog is increased during periods of increased growth velocity and decreased after healing of rickets; the dose is titrated to achieve normal levels of alkaline phosphatase, improve bowing and growth velocity, while avoiding hypercalciuria. Patients with hereditary hypophosphatemic rickets with hypercalciuria show increased 1,25(OH)$_2$D$_3$ synthesis and suppression of PTH; these patients require treatment with phosphate supplements alone. Optimal therapy is indicated by the

resolution of bone pains (within a few weeks), return to normal of levels of alkaline phosphatase (within a few months), increase in growth velocity (in a year) and straightening of legs (in 3–4 years). Increased PTH levels suggest overtreatment with phosphate or under treatment with vitamin D analog. Persistence of leg bowing persists despite *optimal* treatment requires consideration of surgery, preferably beyond growing age.

Patients with VDDR type I require physiological doses of alfacalcidol or calcitriol (1–3 μg/day) along with calcium supplements. Improvement in serum calcium occurs within days, radiologic improvement within 2–3 months while the rickets heals by 9–10 months. Treatment of VDDR type II is challenging with variable response. While some patients respond to very large doses of calcitriol and calcium supplementation, others require prolonged administration of intravenous (IV) calcium to bypass the defect in intestinal calcium absorption. The use of IV calcium may be useful in ameliorating hypocalcemia, hypophosphatemia, secondary hyperparathyroidism and elevated alkaline phosphatase. Phosphate supplements are not required if correction of serum calcium results in improvement in secondary hyperparathyroidism that causes hypophosphatemia. The calcimimetic, cinacalcet has been recently used to control secondary hyperparathyroidism in VDDR type II leading to healing of rickets.

Therapy for RTA is detailed in Chapter 41.14. Patients with distal RTA must receive alkali supplementation as sodium and/or potassium bicarbonate or citrate salts (Polycitra, Shohl's solution) to maintain serum bicarbonate (HCO$_3^-$) concentration greater than 20–22 mEq/L. The requirement of alkali typically decreases from 5–8 mEq/kg/day in infancy to 3–4 mEq/kg/day in childhood and 1–2 mEq/kg/day in adults. Compliance is hindered by the need for multiple daily doses and bitter taste of the citrate solution; palatability is improved by mixing it with water or juice. The excessive use of sodium bicarbonate is counterproductive since it expands extracellular volume and decreases proximal tubular reabsorption of HCO$_3^-$, thereby increasing the need for alkali. Normalization of serum HCO$_3^-$ concentration and growth are good indicators of appropriate treatment. Patients with proximal RTA require alkali at 5–8 mEq/kg/day along with dietary sodium

restriction, and occasionally, hydrochlorothiazide. Patients with Fanconi syndrome require additional phosphate supplementation.

IN A NUTSHELL

1. Vitamin D refractory rickets is a clinical syndrome where there is lack of bone mineralization despite adequate therapy with vitamin D.
2. Clinical signs of refractory rickets include growth failure, bony deformities, bone pain, muscle weakness, polyuria, polydipsia and dental caries.
3. Common causes of nonazotemic refractory rickets in children include RTA, hypophosphatemic rickets and VDDR type I and II.
4. Adequate treatment is associated with satisfactory response in most cases.

MORE ON THIS TOPIC

Bajpai A, Bardia A, Mantan M, et al. Non-azotemic refractory rickets in Indian children. Indian Pediatr. 2005;42:23-30.

Gil-Peña H, Mejía N, Santos F. Renal tubular acidosis. J Pediatr. 2014;164:691-8.

Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122:398-417.

Penido MG, Alon US. Hypophosphatemic rickets due to perturbations in renal tubular function. Pediatr Nephrol. 2014;29:361-73.

Sahay M, Sahay RK. Refractory rickets in the tropics. J Pediatr Endocrinol Metab. 2010;23:597-601.

Schlingmann KP, Kaufmann M, Weber S, et al. Mutations of CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 2011;365:410-21.

Srivastava T, Alon US. Cinacalcet as adjunctive therapy for hereditary 1,25-dihydroxyvitamin D-resistant rickets. J Bone Miner Res. 2013;28:992-6.

Wharton B, Bishop N. Rickets. Lancet. 2003;362:1389-400.

Chapter 41.18
Hypertension
Swasti Chaturvedi

Hypertension is a risk factor for stroke, coronary artery disease and kidney damage in adults. There is a paucity of data about the long-term sequelae of persistent hypertension in children, but it is known that children with hypertension have evidence of end-organ damage and are at risk of hypertension into adulthood. The widespread adoption of National High Blood Pressure Education Program Fourth Report has led to uniformity in classification and management of hypertension. The Indian Society of Pediatric Nephrology (ISPN) has provided guidelines for systematic and careful evaluation of hypertensive children. The incidence of primary hypertension is estimated to be 1–20% and rising among children and young adults.

DEFINITION OF HYPERTENSION

The definition of hypertension in adults is based on the extensive morbidity and mortality data. This allowed correlation of high blood pressure in adults with the adverse events thus making it possible to have relevant *cut-off* measurements. As mentioned previously, there is a paucity of long-term studies looking at effects of pediatric hypertension and hence definitions are just based on normative distribution of systolic and diastolic blood pressure in healthy children **(Table 1)**. This table includes the 50th, 90th, 95th and 99th percentiles by gender, age and height.

Measurement of Blood Pressure

Blood pressure should be measured routinely, at least annually, in all children older than 3 years who seek medical consultation. Children below 3 years with any of the following risk factors should also be screened for hypertension: (1) history of prematurity, very low birthweight babies, or other neonatal complications requiring intensive care; (2) congenital heart disease (repaired or unrepaired); (3) recurrent urinary tract infections, hematuria, or proteinuria; (4) known renal disease or urologic malformation; (5) family history of congenital renal disease; (6) solid organ transplantation; (7) malignancy or bone marrow transplant; (8) treatment with drugs known to raise blood pressure; (9) other illnesses associated with hypertension, e.g., neurofibromatosis, tuberous sclerosis; and (10) evidence of raised intracranial pressure.

Method of Measurement and Devices

Various measurement devices are available. The auscultatory method is preferred, and performed using either the mercury or aneroid sphygmomanometer. The use of the former is discouraged due to the environmental toxicity of mercury. The aneroid sphygmomanometers are quite accurate but need regular calibration. The oscillometric devices measure mean arterial pressure and then use algorithms to calculate systolic and diastolic blood pressure. Advantages of these instruments are their ease of use (especially in infants and younger children and in intensive care setting), no environmental hazard and minimization of observer bias. The disadvantages are that the algorithms used by companies are proprietary and differ among devices; this can result in variations and lack of comparability. These devices also need regular validation and calibration. Blood pressure values exceeding the 90th centile by oscillometric method should be confirmed by an auscultatory technique.

Ambulatory Blood Pressure Monitoring

Blood pressure demonstrates a circadian rhythm and is affected by sleep/wake cycle and activity. A single random blood pressure level thus may not be truly representative; ambulatory blood pressure monitoring (ABPM) provides a more detailed overview. A portable device records systolic and diastolic blood pressure every 20–30 min over 24 hours. Parents or child are instructed to maintain a diary with record of the time of sleeping and time of waking and any activity. The mean blood pressure during the day and night and over 24 hours as well the degree to which blood pressure exceeds the upper limit of normal over a time period (blood pressure load > 25% is considered abnormal) are calculated. Additionally ABPM can detect the phenomenon of *dipping*, the normal physiological drop in blood pressure during sleep. Absent or reduced dipping (< 10%) is seen in children with chronic kidney disease. ABPM is indicated in patients with suspected white coat or masked hypertension, in assessing hypertension risk and if detailed information regarding blood pressure patterns is required (patients with episodic hypertension, chronic kidney disease, diabetes mellitus and autonomic dysfunction).

ETIOLOGY

Hypertension can be primary (essential) or secondary to a renal, cardiac, vascular or endocrine cause. Secondary causes are likely in a younger child and in presence of stage 2 hypertension. Renal parenchymal causes account for 75% and renovascular causes for 10% of secondary hypertension **(Table 2)**. Renal parenchymal disease includes conditions like acute or chronic glomerulonephritis, reflux nephropathy and obstructive uropathy. Renovascular disease may occur due to renal artery stenosis, renal artery thrombosis or Takayasu aortoarteritis. Endocrine causes include pheochromocytoma, neuroblastoma, primary hyperaldosteronism, Cushing syndrome

Table 1 Staging of pediatric hypertension

	Definition
Normal blood pressure	Average systolic or diastolic blood pressure < 90th percentile
Prehypertension	Average systolic or diastolic blood pressure 90th to 95th percentile, or blood pressure > 120/80 mm Hg
Stage 1 hypertension	Average systolic or diastolic blood pressure 95th to 99th percentile plus 5 mm Hg
Stage 2 hypertension	Average systolic or diastolic blood pressure > 99th percentile plus 5 mm Hg
White coat hypertension	Blood pressure > 95th centile when measured in clinic setting but < 90th centile when measured outside clinic environment. This appears to be a prehypertensive condition with risk of ventricular hypertrophy and progression to sustained hypertension
Masked hypertension	Blood pressure normal in clinic setting but in hypertensive range when measured outside clinic environment as detected on ambulatory blood pressure monitoring. This condition is considered more serious than white coat hypertension
Hypertensive urgency	Raised blood pressure without end-organ damage or symptoms, such as headache, nausea or blurred vision
Hypertensive emergency	Raised blood pressure along with presence of end-organ damage, such as encephalopathy, seizures, congestive heart failure, acute kidney injury, papilledema or pulmonary edema

Note that normative data is based on age, height and gender. Definitions are based on blood pressure taken on greater than or equal to three separate occasions. The addition of 5 mm Hg to define stage 2 hypertension is to allow for interobserver differences. Blood pressure tables are applicable for children aged 1 year and older, and should be used when measuring blood pressure by auscultatory method. Normative data for oscillometric devices is also available.

Table 2 Causes of persistent hypertension by age

Newborn	Childhood	Adolescence
Renal vein thrombosis	Renal parenchymal disease (dysplasia, glomerular)	Primary (essential) hypertension
Coarctation of aorta	Renovascular disease	Renal parenchymal disease
Congenital renal anomalies	Coarctation of aorta	Renovascular disease
Renal artery stenosis	Endocrine causes	Endocrine causes
	Primary (essential) hypertension	

and hyperthyroidism. Primary hypertension is a diagnosis of exclusion when no etiology is identified after careful evaluation.

CLINICAL FEATURES

Hypertension is mostly asymptomatic in children. Clinical history taking and examination **(Table 3)** for the underlying etiology should be focused on detecting secondary causes.

INVESTIGATIONS

A careful history and examination is complemented by judicious and targeted use of investigations to identify the cause.

Preliminary Investigations
- Complete blood counts
- Blood electrolytes, creatinine, urea, calcium, phosphorus, bicarbonate, uric acid; urinalysis, urine culture, 24 hours protein
- Chest X-ray, abdominal ultrasound
- Screen for end-organ damage and comorbidities: ECG, echocardiogram, fundus examination, fasting lipid profile and glucose.

Further Investigations

Glomerulonephritis Serum C3, antistreptolysin-O titer (ASO), antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), antineutrophil cytoplasmic autoantibody (ANCA), renal biopsy.

Reflux nephropathy Micturating cystourethrogram, dimercapto-succinic acid scintigraphy.

Renovascular disease Doppler ultrasound, captopril-primed isotope scintigraphy (DTPA or MAG3), renal angiography or digital subtraction angiography, renin sampling from renal veins and inferior vena cava.

Pheochromocytoma Urine and plasma catecholamines, calcitonin, parathormone, metaiodobenzylguanidine (MIBG) scintigraphy, CT and magnetic resonance imaging.

Endocrine causes Urine steroid profile; plasma renin, aldosterone, cortisol, dexamethasone and adrenocorticotropic hormone (ACTH) tests.

Coarctation of aorta Echocardiogram, angiography.

Rarely, single gene disorders can lead to hypertension **(Table 4)**. These conditions should be suspected when there is strong family history, severe and difficult to control hypertension, and presence of electrolyte and acid-base abnormalities.

TREATMENT

Therapy of hypertension depends on severity and cause of hypertension. In general prehypertension and stage 1 hypertension

Table 3 Clues to etiology based on findings on physical examination

Clinical examination	Finding	Possible cause
Height, weight	Growth delay	Chronic illness
Body mass index	Elevated	Obesity in an adolescent suggests primary hypertension; truncal obesity is seen with cushing disease
Heart rate	Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma, primary hypertension
Four limb pulses and blood pressure	Decreased lower limb pulses; low lower extremity pressures	Coarctation of aorta
Eyes	Retinal changes, papilledema	Indicate severe and sustained hypertension
Head and neck	Hirsutism and moon facies	Cushing disease
	Elfin facies	Williams syndrome
	Enlarged thyroid	Hyperthyroidism
	Webbed neck	Turner syndrome
	Tonsil, adenoid hypertrophy	Obstructive sleep apnea
Skin	Pallor, flushing, diaphoresis	Pheochromocytoma
	Rash	Connective tissue disease
	Café-au-lait spots, adenoma sebaceum	Neurofibromatosis, tuberous sclerosis
	Acanthosis nigricans	Type 2 diabetes; metabolic syndrome
Joints	Swelling or tenderness	Connective tissue disease
Chest	Widely spaced nipples	Turner syndrome
	Murmur	Congenital heart disease
Abdomen	Mass	Cystic kidneys, hydronephrosis, Wilms tumor, neuroblastoma
	Bruit	Renal artery stenosis
Genitalia	Ambiguous	Congenital adrenal hyperplasia

Table 4 Monogenic causes of hypertension

Condition	Description	Renin/aldosterone	Potassium	Treatment
Liddle syndrome	Gain of function mutation in ENaC; AD; onset in third decade	Low/low	Low to normal	Amiloride, triamterene
Gordon syndrome	Mutations in gene encoding WNK kinases 1 and 4; AD; onset in second or third decade	Low/low	High, metabolic acidosis	Thiazides, low sodium diet
Glucocorticoid remediable hypertension	Chimeric gene formed from 11β-hydroxylase gene and aldosterone synthase gene results in ACTH stimulating aldosterone synthesis; AD; onset in second or third decade Risk of hemorrhagic stroke from ruptured cerebral aneurysms. Urinary levels of 18-oxosteroids are increased	Low/high	Low to normal	Glucocorticoids
Apparent mineralocorticoid excess	Mutation in gene encoding 11β-hydroxysteroid dehydrogenase; AR; onset in childhood. Nephrocalcinosis and rickets may be noted Ratio of cortisol to cortisone metabolites in the urine is increased	Low/low	Low to normal	Spironolactone, dexamethasone
Congenital adrenal hyperplasia	11β-hydroxylase and 17α-hydroxylase deficiency; AR; onset in childhood	High/high	Low to normal	Glucocorticoids

Abbreviations: ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AR, autosomal recessive; ENaC, epithelial sodium channel.

require institution of nonpharmacological management whereas stage 2 hypertension requires both pharmacological and nonpharmacological management. Hypertensive urgencies and emergencies require urgent recognition and careful lowering of blood pressure in a hospital setting. Surgical treatment is indicated for coarctation of aorta, pheochromocytoma, other endocrine tumors and most forms of renovascular hypertension. **Table 5** outlines the management strategy for children after initial clinic screening.

Nonpharmacological Interventions

Weight reduction results in reduction in systolic and diastolic blood pressure by approximately 1 mm Hg/kg lost; pronounced blood pressure reduction is seen in those with weight loss exceeding 5 kg. Weight loss is associated with an increase in high-density lipoproteins and reduction in triglycerides. Abnormal weight gain should be prevented. *Regular physical exercise* for 30–60 min on most days lowers both systolic and diastolic blood pressures. Sedentary activities should be limited to less than 2 hours a day. *Dietary modification* to consume a low fat and low salt diet is useful. At least five helpings of fruits and vegetables are recommended. The entire family should be involved in lifestyle modifications to have a consistent and sustained effect.

Pharmacological Interventions

Indications of drug therapy are: (1) symptomatic hypertension; (2) secondary hypertension; (3) stage 1 hypertension refractory to lifestyle changes; (4) stage 2 hypertension; and (5) end-organ involvement (proteinuria, retinopathy, left ventricular hypertrophy). Targets for blood pressure reduction depend on the absence or presence of end-organ damage. In the former, the target is to reduce blood pressures to below the 95th percentile, while in the latter the aim is below the 90th percentile.

Hypertensive Emergencies

Prior to commencing antihypertensive therapy, it is important to ensure that elevated blood pressure is not caused by severe pain, increased intracranial pressure or coarctation of aorta because lowering of blood pressure will need to be achieved by different means in these conditions. In patients with hypertensive emergencies, the aim is to reduce blood pressure by 25% during the initial 8 hours of treatment. Excessive reduction should be avoided, since this can result in reduced cerebral blood flow. Accurately titrated intravenous infusions are preferred over oral agents **(Table 6)**.

Pharmacological Agents

Legislative initiatives in the United States and European Union have resulted in increased number of trials on pediatric antihypertensive agents and approval for their use **(Table 7)**.

A recent Cochrane meta-analysis on pharmacological interventions for hypertension found few randomized controlled trials in children. Most studies are of short duration (few weeks) and variable quality. In the absence of good quality evidence, there is no consensus on optimal first-line therapy.

Therapy should be preferably started with a single agent and the dose optimized to achieve the desired reduction in blood pressure. Most experts start with an angiotensin-converting enzyme inhibitor, calcium channel blocker or beta-blocker after ruling out any contraindications to these medications. If a single drug fails to achieve the desired effect then a second drug should be added in a stepwise approach. The antihypertensive agent can be targeted to underlying condition. Some examples of the targeted approach are given in **Table 8**. Drugs affecting the renin-angiotensin-aldosterone system are preferred in children with chronic kidney disease and proteinuria because of renoprotective and antiproteinuric effects.

Table 5 Follow-up after initial blood pressure measurement

	Measure blood pressure	Lifestyle
Normal	Next visit	Normal
Prehypertension	In 6 months	Weight management, physical activity
Stage 1 hypertension	1–2 weeks	Weight management, physical activity
Stage 2 hypertension	Evaluate; refer	Weight management, physical activity

Table 6 Medications used in hypertensive emergencies

	Dose	Side effects
Sodium nitroprusside	0.5–8 μg/kg/min IV infusion	Nausea, arrhythmias, muscle twitching, headache, tachycardia, cyanide toxicity (if used > 72 hours or in renal failure)
Labetalol	0.5–3 mg/kg/hour IV	Pallor, bradycardia; avoid in asthma, heart failure
Esmolol	Load 500–600 μg/kg/min followed by 50–250 μg/kg/min	Blurred vision, confusion, dizziness, increased sweating; avoid if suspected pheochromocytoma
Nifedipine	0.25–0.5 mg/kg oral or sublingual	Flushing, headache, unpredictable hypotension
Hydralazine	0.1–0.5 mg/kg/dose IV slow; can be repeated in 4 hours	Tachycardia, palpitations, flushing, fluid retention

Table 7 Antihypertensive agents

Drug	Dose (oral doses unless specified)	Side effects, comments
Angiotensin-converting enzyme inhibitors (ACEIs)		
Enalapril	0.1–0.6 mg/kg/day QD or BID (max: 40 mg/day)	Cough, angioedema, hyperkalemia; watch for rise in creatinine; avoid use in bilateral renal artery stenosis. Contraindicated in pregnancy: risk of renal tubular dysgenesis, defective skeletal development, death in utero
Benazepril	0.2–0.6 mg/kg/day QD (max: 40 mg/day)	
Lisinopril	0.05–0.6 mg/kg/day QD (max: 40 mg/day)	
Fosinopril	0.1–0.6 mg/kg/day QD (max: 40 mg daily)	
Captopril	0.3–0.5 mg/kg/dose BID or TID	
Angiotensin receptor blockers (ARBs)		
Losartan	0.75–1.4 mg/kg QD (max: 100 mg daily)	Hyperkalemia; watch for rise in creatinine
Irbesartan	75–150 mg/day QD	
Valsartan	1.3–2.7 mg/kg/day QD (max: 160 mg/day)	
Aldosterone receptor antagonist (ARA)		
Eplerenone	25–100 mg/day QD or BID	Hyperkalemia
Beta-blockers		
Atenolol	0.5–2 mg/kg/day QD (max:100 mg/day)	Bradycardia, syncope, lethargy, irritability, depression. Contraindicated in diabetes mellitus, asthma, congestive heart failure, Raynaud phenomenon and atrioventricular septal defects
Propranolol	1–4 mg/kg/day BID-QID (max: 640 mg/day)	
Metoprolol	1–6 mg/kg BID (max: 200 mg/day	
Alpha-blockers		
Prazosin	50–100 μg/kg/day BID-TID (max dose 500 μg/kg/day)	First dose postural hypotension. Phenoxybenzamine and phentolamine are used mostly in pheochromocytoma
Terazosin	0.04–0.4 mg/kg/daily	
Phenoxybenzamine	0.2–0.5 mg/kg BID-TID	
Phentolamine	15 mg/kg in 50 mL dextrose at 1–10 mL/hour IV	
Alpha- and beta-blockers		
Carvedilol	0.1–0.5 mg/kg/dose BID	Pallor, bradycardia; avoid in asthma, heart failure
Labetalol	2–10 mg/kg/day BID	
Calcium channel blockers (CCBs)		
Amlodipine	0.06–0.3 mg/kg/day QD (max: 10 mg/day)	Edema, headache, flushing, tachycardia
Felodipine	2.5 mg/day QD	
Vasodilators		
Hydralazine	0.25–7.5 mg/kg/day TID-QID (max: 200 mg/day)	Tachycardia, headache, salt and water retention; hirsutism with minoxidil
Minoxidil	0.1–1 mg/kg/day BID-TID (max: 50 mg/day)	
Central α-antagonist		
Clonidine	5–20 μg/kg/day QD-BID	Rebound hypertension, hallucinations, depression, sedation, dry mouth
Diuretics		
Hydrochlorothiazide	1–3 mg/kg QD-BID (max: 50 mg/day)	Electrolyte abnormalities, dehydration
Furosemide	0.5–6 mg/kg/day QD-BID	
Amiloride	5–20 mg/day QD	

Abbreviations: BD, twice daily; QD, once daily; QID, four times a day; TID, thrice a day.

Table 8 Suggested choice of antihypertensive drugs based on underlying etiology

Conditions	Medication
Renovascular hypertension	ACEI, ARB, diuretics; ACEI/ARB contraindicated in bilateral renal artery stenosis
Chronic kidney disease with proteinuria, diabetes mellitus with microalbuminuria, obesity related hypertension	ACEI, ARB
Coarctation of aorta, migraine	Beta-blockers
Hypertension related to fluid overload, e.g., acute postinfectious glomerulonephritis	Diuretics (furosemide), CCB; avoid potassium-sparing diuretics and ACEI or ARB in oliguria or severe acute kidney injury

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

IN A NUTSHELL

1. The prevalence of childhood hypertension is increasing.
2. Patients with confirmed hypertension should be evaluated carefully to identify the underlying etiology, determine comorbidities and detect target-organ damage.
3. Therapeutic lifestyle modification should be advised in all hypertensive children.
4. Pharmacologic therapy is required in those with secondary hypertension, stage 2 or symptomatic hypertension and in the presence of end-organ damage.
5. Since there is no consensus on the first-line antihypertensive agent, medications should be prescribed rationally based on the underlying cause and risk of side effects.

MORE ON THIS TOPIC

Bagga A, Jain R, Vijaykumar M, et al. Evaluation and management of hypertension. Indian Pediatr. 2007;44:103-21.

Chaturvedi S1, Lipszyc DH, Licht C, et al. Pharmacological interventions for hypertension in children. Cochrane Database Syst Rev. 2014;2:CD008117.

Gulati A, Srivastava RN. Hypertension. In: Srivastava RN, Bagga A. Pediatric Nephrology. 5th ed. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd.; 2011. pp. 337-59.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555-76.

Chapter 41.19
Urinary Tract Infection and Vesicoureteric Reflux
Pankaj Hari

URINARY TRACT INFECTION

About 2–8% of children suffer from urinary tract infection (UTI) and one-third of children with febrile UTI have vesicoureteric reflux (VUR). It is estimated that approximately 1% of children have VUR, increasing the risk of recurrent UTI. Experimental data suggests that UTI in the presence of VUR causes renal scarring. Renal damage associated with VUR accounts for 7–17% of end-stage renal disease. Early recognition and appropriate management of VUR is expected to prevent development of renal insufficiency.

EPIDEMIOLOGY

The incidence of symptomatic UTI in term and preterm neonates is 1% and 3%, respectively. While girls are more prone to UTI than boys, boys are more susceptible before the age of 3 months. It is estimated that 2% of boys and 7% of girls have one UTI by 7 years. The rate of UTI in uncircumcised boys is several fold higher than in circumcised boys.

ETIOLOGY

Over 80% of community-acquired UTI is caused by *Escherichia coli*. Organisms such as *Klebsiella*, *Proteus*, *Enterobacter*, *Staphylococcus* and *Streptococcus faecalis* are identified in immunocompromised hosts, patients with prolonged urinary catheterization and in nosocomial settings. Infection with *Candida* may be seen in preterm infants, immunocompromised children and following prolonged antibiotic therapy.

PATHOGENESIS

In the neonatal period, renal parenchymal infection usually occurs by hematogenous spread. Ascending infection from the urethra to bladder and the kidneys is common in older children. Direct extension of infection can occur in the presence of fistulas from vagina or intestines to the urinary tract. Irrational antibiotic therapy may lead to fecal recolonization with virulent bacteria thereby predisposing to bacteriuria by disrupting the normal periurethral flora.

CLINICAL FEATURES

The symptoms of UTI in young children are nonspecific and require a high index of suspicion. In neonates, UTI may present with fever, irritability, poor feeding, vomiting, lethargy, jaundice and symptoms of systemic sepsis. Sometimes the child may present with recurrent fever, diarrhea, vomiting, abdominal pain and poor weight gain. Urinary symptoms such as burning, urgency, frequency, flank pain, turbid urine, intermittent voiding dysfunction and a recent onset of enuresis are seen in older children. About 5% of febrile children below 2 years without focus have UTI. It is difficult to predict based on symptoms whether a child has localized cystitis or pyelonephritis. A febrile UTI in young children should be considered as pyelonephritis.

DIAGNOSIS

Urinalysis is helpful in making a presumptive diagnosis of UTI and facilitates initiation of empirical treatment. However, confirmation of the diagnosis on urine culture is mandatory.

Collection of Urine

The specimen for urine culture should be obtained carefully to prevent contamination by commensal flora especially in females. A clean-catch specimen is most widely used in toilet-trained older children. The initial urinary stream washes away distal urethral organisms and should be discarded. In girls, parents should be instructed to part the labia while passing urine. Cleaning of the vulva in prepubescent girls or the meatus in boys is not necessary. Early morning urine samples harbor greater bacterial counts but are less amenable to outpatient practice.

In neonates and infants particularly girls, the best technique for obtaining an uncontaminated specimen is suprapubic aspiration from the bladder. It can be performed safely using a 21-gauge needle, 1–2 cm above the pubic symphysis. Occasionally parents may succeed in collecting a clean-catch sample in a male infant. Urine specimen can also be collected by temporary transurethral catheterization. Bag specimens have unacceptably high contamination rate, even with thorough cleaning of the prepuce or the perineum and are not recommended. A sterile culture from bag specimen is helpful in ruling out UTI. Use of diapers or absorptive pads for collecting urine for culture is not recommended.

In children with indwelling catheters, urine can be aspirated from the catheter using a sterile needle and syringe. Bacteria multiply in the bags and specimen obtained from this site is unsuitable. Obtaining appropriate urine specimen is difficult in patients with ureterostomy or vesicostomy. Catheterization of the stoma under asepsis is recommended and the culture result should be interpreted as any catheter specimen.

The sample should be transported to the laboratory as early as possible. If delay of more than 2 hours is anticipated, the specimen can be stored in a refrigerator at 4ºC for up to 72 hours before plating. This would preserve the white cell count and prevent growth of contaminating bacteria.

Urinalysis

The gold standard for diagnosis of UTI is urine culture. However, a major drawback of urine culture is the time-delay between collection of the specimen and identification of bacterial growth. Urinalysis is a useful screening test and facilitates initiation of therapy in patients with strong suspicion of UTI; however, it cannot be used as a substitute for urine culture. The sensitivity and specificity of various components of urinalysis and newer tests for diagnosing UTI is presented in **Table 1**.

Leukocyturia Presence of greater than 5 white cells/high-power field in a centrifuged urine sample or more than 10 white cells/mm in uncentrifuged urine is found in 80–90% of patients with symptomatic UTI. While leukocyturia may occur in several conditions resulting in inflammation in and around the urinary tract, its absence does not exclude UTI. White cell casts are highly suggestive of acute pyelonephritis. Leukocytes may lyse rapidly if urine microscopy is delayed.

Nitrate reductase It is based on reduction of nitrate to nitrite by nitrate reductase enzyme present in most coliforms. The sensitivity of nitrite test is low in infants who void frequently and have short bladder incubation time. It is also less reliable in young boys in

Table 1 Urinalysis and screening tests for diagnosis of urinary infection

Test	Sensitivity (%)	Specificity (%)
Leukocyte esterase	83	78
Nitrite	53	98
Leukocyte esterase and nitrite	72	96
Leukocyturia	73	81
Bacteria	81	83
Gram stain, any organism	93	95
Catalase	86	75
Lactoferrin	93	89
Bioluminescence	96	70
Turbidimetry	94	55

whom the preputial bacteria may reduce nitrite and give a false-positive result.

Leukocyte esterase A chloroacetate stain reacts with the enzyme leukocyte esterase found in neutrophil granules. Detection of leukocyturia by this test is reasonably sensitive but less specific for UTI. It is more accurate than microscopy because enzyme activity is still retained when white cells have disintegrated. Combination of leukocyte esterase and nitrite dipstick test is highly sensitive and specific for diagnosing UTI.

Detection of bacteriuria Microscopy of uncentrifuged, unstained urine will detect more than 10^4 bacteria/mL of urine. The presence of a single bacterium in a centrifuged or a Gram stained fresh urine specimen has a high sensitivity and specificity for predicting a positive urine culture. However, these methods are labor intensive.

Urine Culture

On culture, the bacterial count is important to differentiate true infection from contamination by periurethral flora. The cut-off figures for significant bacteriuria vary with the method of urine collection **(Table 2)**. Lower bacterial counts may be sufficient to diagnose UTI in children with urinary frequency and in newborns. A urine culture should be repeated in case of mixed growth suggestive of contamination.

Other investigations in patients with UTI include a blood urea, creatinine and leukocyte count. Nonspecific markers of inflammation such as leukocytosis, raised C-reactive protein do not provide confirmatory evidence of pyelonephritis. Photopenic areas on ^{99}Tc-dimercaptosuccinic acid (DMSA) scan indicate inflammation in the renal parenchyma and suggest pyelonephritis. However, detection of acute pyelonephritis by DMSA scan does not change the subsequent management and its routine use in clinical practice is not recommended.

MANAGEMENT

The aim of management of UTI is to prevent renal scarring and its subsequent complications. Younger age and delay in treatment of

Table 2 Method of urine sample collection and diagnosis of urinary infections

Method	Colony forming units per mL
Clean void	$> 10^5$
Transurethral catheterization	$> 10^4$
Suprapubic aspiration	Any
Bag specimen	Not recommended

Note: Lower counts may be acceptable in infants.

UTI are significant risk factors for renal scarring. Differentiation of acute pyelonephritis from cystitis in a child with UTI is difficult. Infants and sick children with suspected UTI should be treated promptly after obtaining urine culture. The choice of antibiotic should be guided by the most likely organism and its local susceptibility pattern. Although community-specific resistance rates among common urinary pathogens may not be readily available, accumulating data suggest that there is a trend towards increasing resistance to commonly used antimicrobial agents for treatment of UTI such as trimethoprim-sulfamethoxazole. Clinically UTI can be classified as complicated or uncomplicated.

Severe or Complicated UTI

The presence of fever greater than 39°C, marked toxicity, persistent vomiting, dehydration and renal angle tenderness suggests complicated UTI. Children less than 3 months of age and those with complicated UTI should be hospitalized and treated with parenteral antibiotics. A third-generation cephalosporin (cefotaxime or ceftriaxone) is preferred **(Table 3)**. Usually a single antimicrobial should be used in community-acquired infections and combinations should be reserved for critical cases. Oral cefixime is as efficacious as parenteral therapy in children with suspected acute pyelonephritis. Intravenous therapy with single daily dose of aminoglycoside has also been found to be safe and effective.

Intravenous therapy is given for the first 2–3 days. Once the result of antimicrobial sensitivity is available, treatment may be modified accordingly. When the clinical condition improves and the child is accepting by mouth, oral antibiotics may be started. Majority of febrile children with UTI have evidence of pyelonephritis, hence febrile urinary infections in young children should be treated for 10–14 days.

Uncomplicated UTI

Children more than 3–6 months of age, who are accepting by mouth and not toxic, may be treated with oral antibiotics **(Table 3)**. For uncomplicated UTI in otherwise healthy children with predominant lower tract symptoms, a 3- to 5-day course of therapy has been found to as efficacious as 7- to 10-day therapy.

Resolution of fever is expected by 48–72 hours with adequate therapy. Even under effective therapy, proven with repeat urine cultures, fever may persist for up to 3 days. Failure to respond to therapy may be due to presence of resistant pathogens, complicating factors, or noncompliance. Ultrasonography should be performed early if the expected clinical response is not observed. Routinely a urine culture to document response to therapy is not necessary and should be repeated only if the patient fails to respond to the therapy.

Genitourinary Imaging after UTI

The aim of imaging studies is to identify urologic anomalies that predispose a child to pyelonephritis and to detect evidence of renal scarring. The studies recommended are renal ultrasonography, either a radiocontrast voiding cystourethrography (VCUG) or direct radionuclide cystography (DRCG), and DMSA scan.

Renal Ultrasonography

Renal ultrasonography has completely replaced intravenous pyelography for assessing the gross anatomy of the urinary tract and it is routinely performed after the diagnosis of first UTI. It is a noninvasive test that can demonstrate the size the shape of the kidneys such as solitary or dysplastic kidney, horseshoe kidney and the presence of ureterocele. It is reliable for diagnosing urinary tract obstruction, which may be present in children with first UTI. Ultrasound (US) is not sensitive enough to detect presence of

Table 3 Antibiotics for treatment and prophylaxis of urinary tract infections (UTIs)

	Drug	Dose (mg/kg/day)	Duration
Uncomplicated UTI or cystitis	Oral Amoxicillin or Amoxicillin/clavulanic acid	30–40 in 3 divided doses	7 days
	Cephalexin	30–50 in 3 divided doses	
	Cefadroxil	30–40 in 2 divided doses	
	Cefixime	10 in 2 divided doses	
	Ciprofloxacin	10–20 in 2 divided doses	
Complicated UTI or pyelonephritis	*Parenteral*		10–14 days
	Gentamicin	5 in single dose	
	Amikacin	15 in single dose	
	Cefotaxime	100 in 3 divided doses	
	Ceftriaxone	75–100 in 1–2 divided doses	
Prophylaxis	*Single oral dose*		
	Cotrimoxazole	1–2 of trimethoprim	
	Nitrofurantoin	1–2	
	Nalidixic acid	15–20	
	Cephalexin	10	
	Cefadroxil	3–5	
	Cefaclor	5–10	
	Cefixime	2	

hydronephrosis or hydroureter secondary to VUR because of the dynamic nature of reflux. It is also poorly sensitive test for acute pyelonephritis and renal scarring.

Cystography

All forms of cystography require catheterization and are invasive with potential risk of UTI. Among all these tests, micturating cystourethrography (MCU) provides more information at the cost of higher radiation.

Micturating Cystourethrography

Micturating cystourethrography is the gold standard for diagnosing VUR. In MCU, bladder is filled with a radiocontrast agent by transurethral catheterization under fluoroscopic guidance and films taken during voiding **(Fig. 1)**. MCU permits grading of VUR defines urethral and bladder anatomy and function. The sensitivity of MCU can be increased by cyclic procedures, i.e., filling the bladder and having the child void two or more times. However, cyclic VCUG involves unacceptably high radiation burden.

Radionuclide Cystography

Direct radionuclide cystourethrography is an alternative for diagnosis and evaluation of VUR **(Fig. 2)**. It has a higher detection rate than MCU at a lower radiation exposure. The setbacks of DRCG are poor anatomical resolution, lack of urethral visualization, restricted grading capability. It is useful for follow-up of VUR because of minimal radiation.

Echo-enhanced cystosonography (EECS) offers a nonionizing method for evaluation of VUR. The procedure requires intravesical administration of an echo-enhancing agent (air-filled microbubbles) through transurethral catheterization. Its use is limited in clinical practice due to its drawbacks.

^{99}Tc-Dimercaptosuccinic Acid Scintigraphy

Renal cortical imaging with DMSA is sensitive and specific for the diagnosis of acute pyelonephritis. It is characterized by decreased radiotracer uptake caused by cortical ischemia and tubular dysfunction during acute infection. It is the most reliable investigation for scarring and also assessing renal function **(Fig. 3)**. For renal scarring, a DMSA scan should be performed preferably after 4–6 months after infection.

Figure 1 Micturating cystourethrography showing marked dilatation of pelvicalyceal system and ureter on right side suggestive of grade V vesicoureteral reflux (VUR)
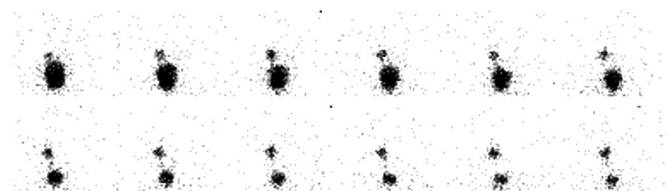
Figure 2 Direct radionuclide cystourethrography (DRCG) showing severe reflux on right side
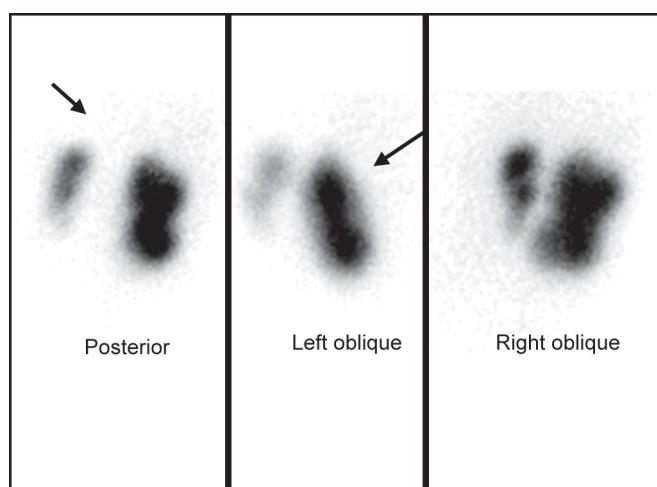
Figure 3 Tc-dimercaptosuccinic acid scan showing irregular renal outline (arrows) suggestive of renal scarring in both kidneys

Recommended Protocols for Evaluation after UTI

All children with UTI should be evaluated to identify those with an underlying urinary tract anomaly. However, UTI is so common that many children with no urinary tract abnormality would be subjected to investigations without benefit. Thus a *high-risk* approach should be followed. The recommendations for imaging following UTI are based on the assumption that early detection of urologic abnormalities especially VUR will lead to improved outcomes. **Table 4** outlines the protocols recommended by the Indian Society of Pediatric Nephrology (ISPN), American Academy of Pediatrics (AAP) and Royal College of Physicians (RCP). Only a few well-designed studies have tested the value of these imaging protocols. The opportunities for prevention of renal damage are most in young children. The ISPN recommends a renal US, MCU and DMSA scan in all children below the age of 1 year. A DMSA scan and renal US are recommended between ages 1 and 5 years. This recommendation is based on the fact that in majority an abnormal DMSA scan provides a clue to the underlying VUR. It is presumed that most vulnerable children would have already developed scars in infancy. Studies in infants have shown that the DMSA scans were abnormal with dilating VUR only.

By pursuing this policy, the number of MCU in this age group is restricted.

Milder reflux that may be missed by this approach, is assumed to not to be contributing to renal scarring. Further imaging with MCU is done if the DMSA scan or US shows abnormal findings. Only renal US is necessary above 5 years of age.

Routine renal US in all children with first UTI is justified in our country where prenatal US is not universal as in developed countries. Children with more than one episode of UTI, irrespective of age, should be evaluated with renal US, DMSA scan and MCU.

RECURRENT UTI

Recurrence after the first UTI is observed in 30–50% of children. Of these a majority occurs within 3 months of the initial episode.

E. coli is the most common organism causing these infections. There is greater incidence of infection by *Proteus, Klebsiella* and *Enterobacter* species in children with recurrent UTI. Recurrent UTIs are more common in infants and are usually caused by previously isolated organism rather than reinfection by new organism. Various predisposing risk factors for recurrent UTI in children are presented in **Box 1**.

PREVENTION

Recurrent UTI may predispose to renal scarring. Prevention is important and antibacterial prophylaxis is indicated in children with recurrent UTI. Underlying risk factors need to be identified and corrected. Interventions that have been associated with a decrease in incidence of UTI include relief of constipation and voiding dysfunction. Currently available probiotics are not recommended to treat or prevent UTI.

Antibiotic Prophylaxis

Although the evidence of benefit of long-term low-dose antibiotic prophylaxis for prevention of UTI is not very strong, it is the most widely used strategy to prevent UTI in clinical practice. Antibiotic prophylaxis is recommended in (1) children with VUR; and (2) those with recurrent febrile UTI even if the urinary tract is normal. Medications used for prophylaxis **(Table 3)** are usually given as single bedtime dose.

The ideal antibiotic for prophylaxis should have a broad spectrum of action and achieve a high urinary concentration with minimal alteration of the bowel flora. The precise mechanism of action of low-dose antibiotic prophylaxis is not known. Nitrofurantoin and cotrimoxazole are the most commonly used drug for long-term prophylaxis. UTI during antibiotic prophylaxis (breakthrough UTI) may result from noncompliance or development of bacterial resistance, mainly occurring with trimethoprim. Nitrofurantoin is associated with nausea and vomiting that may result in discontinuation of therapy in a significant proportion of patients. Cephalexin is preferred in young infants and those with deficiency of the enzyme, glucose-6-phosphate-dehydrogenase. Amoxicillin, nalidixic acid and other quinolones should be avoided for prophylaxis because intestinal colonization with *E. coli* resistant to these agents occurs rapidly. Reinfection of the urinary tract with these resistant bacteria may then occur. Low-dose cefixime is also effective and safe in the prophylaxis of recurrent UTI.

ASYMPTOMATIC BACTERIURIA

It is defined as significant bacteriuria in the absence of symptoms of UTI. The frequency of asymptomatic bacteriuria is about

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BOX 1 Risk factors for recurrent urinary tract infection (UTI)

- Female sex
- Obstructive uropathy
- Severe (grade III–V) vesicoureteric reflux
- Repeated pyelonephritis
- Voiding dysfunction
- Constipation
- Repeated catheterization in neurogenic bladder.

Table 4 Imaging protocols following first urinary tract infection (UTI)

	US	*VCUG*	*DMSA scan*
Indian Society of Pediatric Nephrology	All	< 1 year	< 5 years
*American Academy of Pediatrics	< 2 years	< 2 years	Not recommended
Royal College of Physicians London	All	< 1 year	1–7 years

*Recommendations for < 2 years old only.
Note: Perform all [ultrasonography (US), voiding cystourethrography (VCUG) and Tc-dimercaptosuccinic acid (DMSA)] if any of the above test is abnormal.

1% in girls and 0.05% in boys. The organisms isolated in most cases are usually *E. coli* that of low virulence. The condition is benign and does not cause renal injury. It has been shown to remit spontaneously with time. However, eradication of these nonpathogenic organisms may be followed by symptomatic infection with more virulent strains. Use of antibiotics to treat asymptomatic bacteriuria or antibiotic prophylaxis is therefore not indicated even in the presence of VUR.

VESICOURETERIC REFLUX

Vesicoureteric reflux is a retrograde flow of urine from the bladder into the ureter. It is seen in 30–50% children and 40–50% of infants with UTI. It may predispose to renal parenchymal infection by allowing ascent of bacteria from bladder to the upper urinary tract. VUR is categorized as primary or secondary.

ETIOLOGY

Primary VUR is attributed to an abnormally short intravesical segment of ureter which does not allow its constriction at the ureterovesical junction by contracting detrusors, resulting in reflux. Secondary VUR is due to increased bladder pressures such as those seen with urethral valves and neurogenic bladder.

PATHOGENESIS

There is a strong inheritance pattern for primary VUR. The chance of a sibling of a child with VUR having reflux is about 25%. If one of the parents had a VUR, there is 25–50% increased risk of reflux in offspring. The reflux is usually of low grade and an increased risk of UTI has not been shown in these patients. Age of sibling below 2 years, twin relationship and absence of dysfunctional voiding in index patient have been identified as risk factors for detecting reflux in siblings. A genetic basis for VUR seems evident from the familial clustering of cases in predominantly autosomal dominant, but also in autosomal recessive, X-linked and polygenic patterns. VUR may be associated with developmental malformations of other organs such as eye, ear and face and is termed as syndromic VUR. Several genes have been identified for this form of VUR. Some of the candidate genes found to be associated with primary nonsyndromic VUR include *ROBO2*, *SOX17*, *UPK3A* and *AGTR2*; however, the association is inconsistent suggesting genetic heterogeneity underlying this disorder.

Reflux Nephropathy

Primary VUR is associated with renal scarring which is termed as reflux nephropathy. Experiments have shown that reflux of infected urine can cause renal parenchymal inflammation and scarring. However, severely scarred or shrunken kidney associated with VUR is now believed to be renal dysplasia secondary to fetal reflux and is not secondary to UTI. Children with renal dysplasia mostly have severe grade of VUR; some of whom have never had UTI.

CLINICAL FEATURES

Vesicoureteric reflux is most commonly diagnosed after evaluation for a UTI. However, it may also be detected in asymptomatic children with antenatally diagnosed hydronephrosis and screening of siblings of patients with VUR. It is also diagnosed during evaluation for hypertension, small contracted kidney or chronic kidney disease. While it is more commonly reported in girls presenting with UTI in the West, boys are more often affected in Asia. Presentation with antenatal hydronephrosis is seen common in boys and is associated with severe grades of reflux and scarring.

DIAGNOSIS

The gold standard for diagnosis of VUR is MCU. The approach to diagnosis of VUR in a child following UTI is discussed above. The severity of VUR is graded using the International Study Classification from grade I–V based on the appearance of the urinary tract on contrast MCU as shown in **Figure 4**. Renal US has 50–60% sensitivity for diagnosing VUR. Routine screening of siblings of patients with reflux using VCUG is not done universally. Siblings of children with VUR may be screened using US. The benefit of screening for VUR in asymptomatic siblings is unclear.

The presence of moderate to severe reflux is associated with risk for acute pyelonephritis and reflux nephropathy. Severely scarred can be diagnosed on ultrasonography. Intravenous pyelography is low sensitivity for diagnosing renal scarring and is not indicated for diagnosing reflux nephropathy. DMSA scan is the most sensitive test for detecting small scars. However, since result of DMSA scan does not influence the management of VUR and it has radiation exposure, regular scanning is discouraged.

Bladder-Bowel Dysfunction and VUR

There is increasing evidence that bladder and bowel dysfunction may be found in a significant proportion of children with VUR. Symptoms of unstable bladder include frequency, urgency, incontinence and holding maneuvers. Patients with uncoordinated bladder show urgency, hesitancy and, diurnal and nocturnal incontinence. About one-third of children with bladder dysfunction may be asymptomatic.

All patients with VUR should be assessed for bladder and bowel dysfunction. A detailed history including voiding pattern and bowel habits is important. Constipation is a proven risk factor for recurrent UTI. Examination of lower back should be done for spinal dysraphism. Findings on MCU and US may suggest bladder

| Grade I | Grade II | Grade III | Grade IV | Grade V |
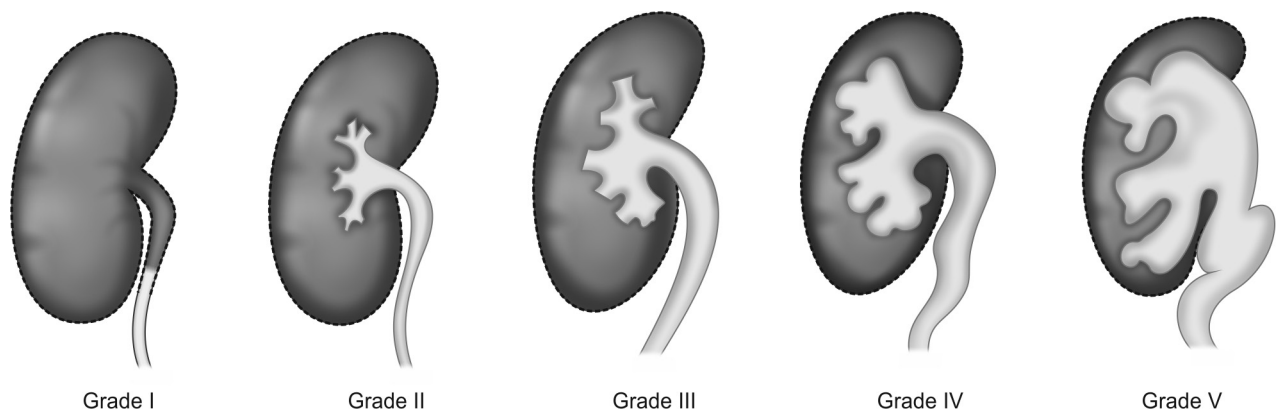
Figure 4 International reflux study grading of vesicoureteral reflux (VUR). *Grade I:* Reflux into the ureter only; *Grade II:* Reflux into nondilated pelvicalyceal system; *Grade III:* Dilatation of ureters and pelvicalyceal sytem; *Grade IV:* Extensive dilation with blunting of calyces with intact papillary impression and tortuosity of ureter; *Grade V:* Massive dilatation of collecting system with clubbing of calyces and loss of papillary impressions and tortuosity of ureter

Table 5 Management and follow-up of primary vesicoureteral reflux (VUR)

VUR grade	Management	Follow-up
I–II	Antibiotic prophylaxis until 1-year old	Observation Restart prophylaxis if breakthrough febrile UTI
III–V	*< 5 years of age:* Antibiotic prophylaxis *> 5 years of age:* Prophylaxis continued if bowel bladder dysfunction	Consider surgery if breakthrough febrile UTI; alternatively, consider a change of antibiotic

dysfunction. Urodynamic study is necessary if bladder dysfunction is clinically suspected.

MANAGEMENT

Traditional treatment of VUR has been surgical reimplantation until it was discovered that children with VUR may do well with low-dose antibiotic prophylaxis. There is strong evidence suggesting that the incidence of recurrent UTI, renal growth and progression or appearance of new scars among patients treated with prolonged antibiotic prophylaxis versus surgical reimplantation is similar. Medical management is therefore regarded as effective as surgery with no clear benefits of surgery over it. The guidelines of ISPN are summarized in **Table 5**.

Antibiotic Prophylaxis

Antibacterial prophylaxis while awaiting spontaneous resolution of VUR is the cornerstone of treatment. This treatment usually suffices for most patients and has been found to be as effective as surgical reimplantation. Surveillance urine cultures, in asymptomatic patients, are not necessary. Treatment of asymptomatic bacteriuria even in patients with VUR is not required and may be harmful. However, urine cultures should promptly be obtained in presence of symptoms. Symptomatic UTI in children with VUR should be treated promptly. Parents should be educated to maintain a high index of suspicion for subsequent UTI.

Patients should be monitored for physical growth and hypertension. Compliance with antibiotic prophylaxis should be ensured on follow-up visits. Investigations include urinalysis, yearly estimation of blood urea and creatinine. Yearly US examination is done to monitor the renal growth. DRCG scan may be done during follow-up to assess resolution in high-grade reflux. A DMSA scan during follow-up may be of prognostic significance. The optimum duration of prophylaxis is not clear. It can also be stopped in a child with low-grade reflux, after 5 years of age in the absence of breakthrough UTI and bladder-bowel dysfunction.

Surgical Reimplantation

Currently the indications of surgery are limited. Recurrences of UTI (breakthrough infections), formation of new scars and decreased renal function may no longer be considered as indications for surgical repair. Surgical correction may be considered in patients with: (1) persistent severe reflux; (2) noncompliance with medical management; (3) parental preference for surgery over prolonged antibiotic prophylaxis; and (4) deterioration of function during antibiotic prophylaxis in a previously normal kidney. Urodynamic evaluation is preferable prior to surgical repair. Surgery is also necessary in patients where VUR is secondary to obstruction (e.g., posterior urethral valves), ureteral duplications or paraureteric diverticuli.

Endoscopic Injection

Endoscopic injection of implant material dextranomer/hyaluronic acid polymer (Deflux), in the submucosal ureteric tunnel, has been advocated for correction of reflux. It has been proposed as an alternative to antibiotic prophylaxis or surgery for persistent VUR. However, the success rate is variable, sometimes requiring multiple injections depending upon the expertise of the urologist.

Further significant proportion of patients may develop recurrence of VUR on long follow-up.

PROGNOSIS

Majority of primary VUR including severe grades resolve completely or become less severe as the child grows. The chances of resolution are highest with low grades of reflux. Untreated bladder-bowel dysfunction is associated with persistence of reflux.

Long-term studies have shown that small scars associated with primary VUR are unlikely to cause hypertension and renal failure. Children with VUR and renal dysplasia are at risk of developing hypertension and end-stage renal failure in later life.

IN A NUTSHELL

1. The symptoms of UTI may be nonspecific and require high index of suspicion.
2. Urinary tract infection should be diagnosed and treated promptly to prevent renal scarring.
3. Urinalysis is helpful in making a presumptive diagnosis of UTI but is not a substitute for urine culture; combination of leukocyte esterase and nitrite reductase is sensitive and specific for diagnosing UTI.
4. Majority of febrile children with UTI have acute pyelonephritis which need not be documented by DMSA scan in clinical practice.
5. Febrile UTI in young children should be treated for at least 7–14 days; uncomplicated lower tract infection in older children may be treated for 3–5 days.
6. Almost one-third to half of all patients with UTI has VUR; all children with first UTI should be evaluated using a high-risk approach.
7. Voiding dysfunction and constipation are important causes of recurrent UTI.
8. Asymptomatic bacteriuria is not harmful and should not be treated.
9. The cornerstone of therapy for primary VUR is antibiotic prophylaxis.
10. While secondary VUR should be treated surgically, indications of surgery for primary VUR are limited.

MORE ON THIS TOPIC

Bagga A, Hari P. Vesicoureteric reflux and reflux nephropathy. Indian Pediatr. 1998;35:1197-209.

Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol. 2009;6:481-9.

Graham JC, Galloway A. ACP Best Practice No. 167: the laboratory diagnosis of urinary tract infection. J Clin Pathol. 2001;54:911-9.

Indian Society of Pediatric Nephrology, Vijayakumar M, Kanitkar M, Nammalwar BR, Bagga A. Revised statement on management of urinary tract infections. Indian Pediatr. 2011;48:709-17.

Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. 2011;15:CD001532.

Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128:595-610.

Chapter 41.20
Dysfunctional Voiding
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The symptoms of bedwetting, incontinence and recurrent urinary tract infections with bladder related symptoms such as urgency, frequency and straining during micturition might result from an underlying anatomical anomaly or a neurological disorder affecting the lower urinary tract, which at times may be occult. However, the symptoms may occur in the absence of either, in which case it is defined as *dysfunctional voiding.* These disorders have a multifactorial etiology. The prevalence of daytime urinary incontinence is around 7–8%. Genetic basis has been reported for some conditions, e.g., urofacial (Ochoa) syndrome, with loss of function mutation in the heparanase 2 gene presenting with a non-neurogenic neurogenic bladder and typical facial grimace when smiling.

CLASSIFICATION OF VOIDING DISORDERS

The International Children's Continence Society (ICCS) in 2006 recommended the use of standard nomenclature for voiding disorders in children **(Table 1)**.

ANATOMY AND INNERVATION OF URINARY BLADDER

The urinary bladder consists of a balloon-shaped reservoir with an outlet at the neck which continues into the urethra. The bladder outlet has two sphincters: (1) the internal sphincter constituted by the detrusor muscle and elastic fibers and (2) the external sphincter constituted by the pelvic floor skeletal muscle. The two important functions of the urinary bladder of (1) storage and (2) evacuation are controlled by a complex neuromyogenic system. The parasympathetic system is responsible for bladder emptying by inducing contraction of the detrusor and relaxation of the internal sphincter. The sympathetic system is responsible for relaxation of the bladder and contraction of the sphincter, ensuring continence during the filling phase. The somatic efferent nerve innervates the external sphincter. The sensation of bladder distention is transmitted by the afferent myelinated fibers. The central pontine micturition center coordinates detrusor contraction and sphincter relaxation that results in voiding. Cortical control is through the anterior cingulate gyrus. Voiding is initiated in the cerebral cortex through relaxation of the external sphincter, followed by inhibition of sympathetic and increase in parasympathetic activity resulting in detrusor contraction with relaxation of the internal sphincter.

Table 1 Definitions for lower urinary tract symptoms

Terminology	Definition
Decreased daytime voiding frequency	Three or fewer voids per day
Increased daytime voiding frequency	Eight or more voids per day
Polyuria	24 hours urine output > 2 L/m^2 body surface area (BSA)
Expected bladder capacity	Age related expected maximum voided volume (MVV), as determined by the formulae: Children > 2 years: [30 + (age in year × 30)] mL; Children < 2 years: [wt. in kg × 7] mL
Nocturnal polyuria	Overproduction of urine at night, defined as nocturnal urine output > 130% of bladder capacity for age
Incontinence	Uncontrollable leakage of urine
Continuous incontinence	Continuous leakage of urine
Intermittent incontinence	Leakage of urine in discrete portions during the day and or night
Urge incontinence	Incontinence when experiencing urgency
Voiding postponement	Incontinence in the presence of habitual holding maneuvers
Enuresis	Incontinence of urine while sleeping
Monosymptomatic enuresis	Enuresis without other lower urinary tract symptoms
Nonmonosymptomatic enuresis	Enuresis with lower urinary tract symptoms such as daytime incontinence, urgency and holding maneuvers
Primary enuresis	Enuresis in a child who is previously dry for < 6 months
Secondary enuresis	Enuresis in a child who is previously dry for > 6 months
Overactive bladder	Condition in patients experiencing urgency symptoms
Underactive bladder	Low voiding frequency; need to increase intra-abdominal pressure to void (lazy bladder)
Dysfunctional voiding	Habitual contraction of the urethral sphincter during voiding, as observed by uroflow measurements
Maximum voided volume	Largest voided volume documented in a bladder diary; replaces the term functional bladder capacity. MVV < 65% of expected bladder capacity suggests small capacity; MVV > 150% of expected bladder capacity indicates large capacity
Detrusor underactivity	Cystometric observation of a contraction of decreased strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying
Detrusor overactivity	Cystometric observation of involuntary detrusor contractions during the filling phase
Residual urine	Urine left in the bladder after voiding. Residual urine in excess of 20 mL or > 10% of expected bladder capacity indicates incomplete bladder emptying

MATURATION OF BLADDER CONTROL

At birth micturition is spontaneous as a spinal cord reflex. Between 1 year and 2 years of age, the bladder capacity increases along with neural maturation of the cortical center. The sensation of bladder filling is present but voiding occurs still as a reflex. During 3–4 years of age micturition can be delayed by voluntary use of the external sphincter, resulting in daytime continence. By 5 years, the child is dry by night and true cortical inhibitory control is achieved. The final step in maturation is when a child is able to void at will even if the bladder is not full. Majority of children are dry during the day by 2–3 years and at night by 3–4 years. Fecal continence precedes urinary continence.

VOIDING DISORDERS

These are defined as functional, abnormal patterns of micturition in the presence of intact bladder innervation and without any congenital or anatomical anomaly of the lower urinary tract. These may be classified as:

Filling phase disorder An overactive bladder with or without incontinence.

Evacuation phase disorder Dysfunctional voiding.

Over a period of time, a dyssynergic bladder that contracts against a closed external or internal sphincter may result in a low pressure hypotonic underactive bladder, leading to overflow incontinence. Severe bladder sphincter dyssynergia is noted in the Hinman syndrome where the urinary bladder is trabeculated, develops a high pressure state with bilateral vesicoureteric reflux and a large postvoid residue akin to neurogenic bladder without an obvious underlying neurological abnormality. The condition requires early diagnosis and treatment as high retrograde pressures invariably lead to renal failure.

Bowel Bladder Dysfunction

This term describes the subset of children with both bladder and bowel voiding difficulties. Many children with bladder problems may reduce fluid intake to minimize wetting, and powerful pelvic floor muscle contractions lead to postponement of defecation and constipation. This further worsens bladder functioning. On the other hand, children with functional constipation may have an increased risk for voiding disorders and urinary infections. In severe situations, children present with fecal incontinence or encopresis.

CLINICAL FEATURES

Primary monosymptomatic nocturnal enuresis presenting with bedwetting needs to be differentiated from the more complex voiding disorders. An overactive bladder presents with increased frequency of voiding, urgency of micturition and holding maneuvers with or without dampness of the underpants due to urge incontinence. These holding maneuvers are also seen in children who habitually postpone voiding; symptoms are aggravated in the evening when the pelvic floor muscles are fatigued. The child with dysfunctional voiding may present with recurrent urinary tract infections, straining to void and lower abdominal pain. Constipation, in almost two-thirds of children with voiding disorders, further worsens bladder functioning. Psychological comorbidity or behavioral disturbances are often noted.

EVALUATION

The first step is to differentiate monosymptomatic primary nocturnal enuresis from a voiding disorder. Clinical examination is required to exclude a neurological or an anatomical basis. This includes examination of back to rule out spinal and sacral anomalies and the abdomen for palpable bladder or kidneys. The lower limbs are assessed for tone, power and sensations, and perineum and external genitalia examined for ectopic ureters, epispadias in boys and vaginal pooling or labial adhesions in girls. A clinical management tool aids history taking **(Box 1)**.

INVESTIGATIONS

A voiding diary is an important component of evaluation that helps ascertain the nature of the problem. It is recommended that the diary be maintained over a minimum of 2–3 days for accuracy, preferably during holidays. Bedwetting diary should be maintained for seven consecutive nights to assess the severity of the problem, detect the presence of nocturnal polyuria and differentiate voiding disorder from monosymptomatic enuresis. **Table 2** lists investigations that are indicated for a child with a voiding disorder. Detailed history, using the clinical management tool, voiding diary and ultrasonography of the abdomen is sufficient in most children.

Detrusor overactivity presents as an overactive bladder with nocturnal enuresis, daytime symptoms, holding maneuvers, small frequent voiding pattern, and a small capacity bladder with insignificant postvoid residue. Dysfunctional voiding due to a bladder sphincter dyssynergia is associated with straining, large capacity bladder and significant postvoid residue. Invasive urodynamic studies are difficult in young children, and not routinely required. Indications for the investigation are: (1) suspected neurologic abnormality; (2) urinary and fecal incontinence; (3) trabeculations of bladder and funneling of sphincter on micturating cystourethrography; (4) failure to respond to therapy for voiding disorder diagnosed using noninvasive assessment.

TREATMENT

The treatment of monosymptomatic nocturnal enuresis is motivation with rewards for dry nights and behavioral therapy

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BOX 1 Checklist of clinical management tool

Refer for evaluation if any of the following symptom is present in a child with enuresis
- Symptoms suggestive for underlying bladder dysfunction
  - Leakages of urine during the day
    - Drops of urine in the under pants
    - Very wet under pants
  - Intermittent or continuous leakage every day?
  - History of daytime incontinence after 3½ years of age
  - Urinary frequency (number of voids during the day; abnormal if < 3 or > 8)
  - Sudden and urgent need to urinate
  - Holding maneuvers observed
  - Needs to push in order to urinate
  - Interrupted urinary stream, or several voids, one after another
- History of urinary tract infection
- Illness and/or malformation
  - Kidneys and/or urinary tract
  - Spinal cord
- *Bowel movements:* Presence or history of either of the following
  - Constipation
  - Traces of feces in the underpants
- *Psychological, behavioral or psychiatric problems:*
  - Evidence of attention deficit hyperactivity syndrome or autism
  - History of motor and/or learning disabilities or delayed development
- *Drinking habits:*
  - Quantity and type of fluid intake
  - Drinks more than one glass during the evening
  - Drinks during the night.

Table 2 Investigations for children with dysfunctional voiding

Investigation	Abnormality detected	Inference
Urinalysis	Glucosuria	Consider diabetes mellitus
	Proteinuria (++ or more)	Consider chronic kidney disease
	> 10 leukocytes per high-power field	Consider urinary infection
Ultrasonography of kidneys and urinary bladder	Bladder wall thickness > 2 mm	Neurogenic bladder, bladder outlet obstruction
	Significant postvoid residue	Incomplete voiding, vesicoureteric reflux, bladder outlet obstruction
	Bladder wall irregularity	Recurrent urinary infection or cystitis
	Hydroureteronephrosis	Obstructive uropathy, vesicoureteric reflux
	Small shrunken kidney(s)	Chronic kidney disease
	Calculi, nephrocalcinosis	Obstructive uropathy
Micturating cystourethrography	Bladder wall irregularity; elongation of bladder shape	Overactive bladder
	Filling of the posterior urethra; spinning top configuration of bladder	Dysfunctional voiding
Magnetic resonance imaging of lumbosacral spine	Tethered cord, diastematomyelia, spine trauma, tumors, degenerative disorders	Neurogenic bladder

using the alarm. Medications are useful in case of an overactive bladder. In children with a voiding disorder, the basis of treatment lies in the exclusion of a neurological cause, treatment of urinary tract infection and (re)-institution of a structured timely voiding pattern with good hydration and hygiene. Treatment of constipation is possible by simple measures like increasing fluid intake, increasing intake of dietary fiber and use of husk (*isabgol*) or lactulose. Nonabsorbable polyethylene glycol powder is easy to prepare and administer.

Overactive bladder is treated with an anticholinergic medication like oxybutynin starting at 2.5 mg to a maximum dose of 15–20 mg/day in three divided doses. Side effects like blurring of vision, headache and diarrhea may be less with tolterodine, at a dose of 1 mg twice daily for children aged 5–10 years. Newer medications like solifenacin, capsaicin and resiniferatoxin and intravesical injection of botulinum toxin are being evaluated to further reduce side effects.

Biofeedback therapy aids retraining children to develop relaxed voiding. Behavioral intervention comprising patient education, scheduled voiding regimen with gradual increasing intervals, urgency control strategies, self-monitoring, and positive reinforcement helps children learn to relax the pelvic floor muscles. Deep breathing exercises, using a relaxed posture and enough time to void while keeping the palms over the abdominal wall are useful. Explaining pelvic floor relaxation exercises to the child and mother with repeated reinforcement is required.

Combination of biofeedback and alpha-blockers like doxazosin (0.5–1 mg/day) has been found useful in patients with dysfunctional voiding. In children with severe dysfunctional voiding and large postvoid urine, clean intermittent catheterization is instituted. Surgical intervention for dysfunctional voiding is reserved for patients who have failed all medical interventions. For children who need bladder emptying but have difficulty in performing clean intermittent catheterization per urethra, an alternative route can be surgically created using the appendix as a conduit in the Mitrofanoff technique. For patients with severe detrusor instability and small capacity bladders, augmentation cystoplasty may be useful.

IN A NUTSHELL

1. Voiding disorders are functional, abnormal patterns of micturition in the presence of intact innervation and without any congenital or anatomical abnormality of the urinary bladder.
2. These are essentially either filling phase disorders with an overactive bladder or evacuation disorders with dysfunctional voiding.
3. Voiding disorders need to be suspected in children presenting with enuresis; history of daytime symptoms should be elicited.
4. Detailed history, clinical examination, voiding diary and abdominal ultrasonography are sufficient in most cases.
5. Treatment of constipation, medications for an overactive bladder and reinstitution of a regular voiding pattern are key components of management.

MORE ON THIS TOPIC

Ansari MS, Srivastava A, Kapoor R, et al. Biofeedback therapy and home pelvic floor exercises for lower urinary tract dysfunction after posterior urethral valve ablation. J Urol. 2008;179:708-11.

Jansson UB, Hanson M, Sillén U, Hellström AL. Voiding pattern and acquisition of bladder control from birth to age 6 years—a longitudinal study. J Urol. 2005;174:289-93.

Kanitkar M, Ramamurthy HR. Bed wetting—silent suffering: an approach to enuresis and voiding disorders in children. Indian J Pediatr. 2013;80:750-3.

Kasirga E, Akil I, Yilmaz O, et al. Evaluation of voiding dysfunctions in children with chronic functional constipation. Turk J Pediatr. 2006;48:340-3.

Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardization Committee of the International Children's Continence Society. J Urol. 2006;176:314-24.

Ramamurthy HR, Kanitkar M. Non-invasive urodynamic assessment in children—are they reliable? Validation of non-invasive urodynamics in children with functional voiding disorders. Indian J Pediatr. 2010;77:1400-4.

Vande Walle J, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis. Eur J Pediatr. 2012;171:971-83.

Chapter 41.21
Chronic Kidney Disease
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Chronic kidney disease (CKD) is often silent until the disease has progressed to a very advanced stage. Therefore, early diagnosis is important to slow the progression of disease and minimize its associated morbidity and mortality. The kidney disease outcomes quality initiative (KDOQI) by the national kidney foundation (NKF) in the United States has published sets of evidence-based guidelines related to the care of adult and pediatric patients with CKD. In conjunction with the NKF, an international working group, the Kidney Disease Improving Global Outcome (KDIGO) initiative, has contributed tremendously to develop similar guidelines at an international level with the aim of improving care for this high-risk population.

DEFINITIONS

Chronic kidney disease is defined as any abnormality of kidney structure or function present for more than 3 months and is classified based on glomerular filtration rate (GFR) **(Table 1)**. Structural or functional abnormalities include any one of the following: abnormalities related to kidney function on blood tests, urinary abnormalities, abnormalities on imaging studies of the kidney, or pathology on a kidney biopsy. This classification system cannot be applied to very young children, until 2 years old, since the body surface area adjusted GFR does not approach adult values until that time.

Measurements of GFR traditionally have been made by determining clearance of creatinine or other markers such as inulin or iothalamate. An alternative and more convenient approach is to estimate GFR (eGFR) using one of many calculations **(Table 2)**.

EPIDEMIOLOGY

The incidence and prevalence of CKD in children are not well established since disease registries focus on those who have end-stage renal disease (ESRD). The ESRD population represents a very small fraction of all those with CKD since children in early stages of CKD may be asymptomatic or have mild symptoms and therefore not seek care. The magnitude of CKD can be extrapolated using population-based studies, which estimate the prevalence of CKD stage 1–4 in adults to be 10.8%, approximately 50 times the prevalence of ESRD (0.2%).

The United States, New Zealand and Austria have high incidence of pediatric ESRD, reportedly 12.4–14.8/million people while Japan had the lowest at 4.3/million people. The incidence and prevalence of ESRD and CKD in children in India is unknown as there are no regional disease registries. Studies are primarily from referral centers; which suggest that most children present in more advanced stages, as many as one-half presenting in ESRD.

ETIOLOGY

The etiology of CKD in children is quite different compared to adults in whom diabetes and hypertension are the most common causes. The causes in children are more varied. There is a predominance of congenital anomalies of the kidney and urinary tract (CAKUT), especially in the younger children. With increasing age, glomerular diseases assume greater importance.

PROBLEMS AND MANAGEMENT

Children with CKD may present with signs and symptoms of the underlying disease that is causing renal injury, such as hematuria, edema or oliguria in the setting of glomerulonephritis, or urinary tract infections and enuresis in children with CAKUT. Many children with CAKUT are now identified prenatally, due to the practice of obtaining routine screening prenatal ultrasounds during pregnancy. However, CKD is often clinically silent. Patients with structural renal anomalies are often nonoliguric and might escape recognition.

Anemia

Anemia is common in all stages of CKD and nearly universal in patients with advanced stages. Findings from the CKiD study, a prospective cohort study in North America, determined that above a GFR of 43 mL/min/1.73 m^2, hemoglobin fell by 0.1 g/dL for every 5 mL/min/1.73 m^2 decrease in GFR. Below an eGFR of 43 mL/min/1.7 3m^2, the hemoglobin declined by 0.3 g/dL for every 5 mL/min/1.73 m^2 decline in GFR. Anemia is multifactorial in origin, though the primary cause is decreased erythropoietin production by peritubular fibroblasts of the renal cortex. Another contributor is iron deficiency, caused by nutritional deficiency, increased blood loss (platelet dysfunction, frequent phlebotomy or blood loss in the dialysis tubing) and poor iron absorption. Other causes of anemia include short erythrocyte survival, deficiencies of B12 or folate, bone marrow suppression from hyperparathyroidism and chronic inflammation.

The evaluation of anemia in children with CKD includes complete blood cell count with red cell indices, absolute reticulocyte count, serum ferritin, folate and B12, and transferrin saturation. Anemia of CKD is usually normochromic and normocytic with normal reticulocyte count. Treatment of anemia includes iron replacement as well as administration of erythropoietic stimulating agents, specifically intravenous (IV) or subcutaneous (SC) recombinant human erythropoietin or an analog of erythropoietin, darbepoetin, which has a longer half-life. Use of these agents has dramatically decreased the need for blood transfusions in patients with CKD. A target hemoglobin for adult patients with CKD of less than 11.5 g/dL is recommended; target hemoglobin for children is 11–12 g/dL.

Mineral and Bone Disorders

Disorders of calcium-phosphate homeostasis are common in children with CKD and lead to abnormalities of bone turnover

Table 1 Definition of chronic kidney disease in children

Category	GFR (mL/min/1.73 m^2)	Action plan
Stage 1	≥ 90	Identify, treat and slow progression of underlying condition
Stage 2	60–89	
Stage 3	30–59	Evaluate and treat complications of CKD
Stage 4	15–29	Prepare for kidney replacement therapy
Stage 5	< 15 or on dialysis	Kidney replacement therapy

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease.

Table 2 Pediatric glomerular filtration rate (eGFR) estimating equations

Creatinine-based equation	eGFR, mL/min/1.73 m^2 = 41.3 x (height, m/serum creatinine, mg/dL)
Cystatin C-based equation	eGFR, mL/min/1.73 m^2 = 70 x (serum cystatin, mg/L)$^{-0.931}$

and poor linear growth. Factors that contribute to these disorders include decreased 1,25(OH) vitamin D_3 synthesis and decreased renal phosphate excretion. Normally, the kidney converts 25(OH) vitamin D_3 to its active form, 1,25(OH) vitamin D3 via 1α-hydroxylase. 1,25(OH) vitamin D_3 increases intestinal absorption of calcium. Early in CKD, fibroblast growth factor 23 (FGF23), a circulating peptide made in the osteoclasts with phosphaturic properties, is increased and suppresses 1α-hydroxylase expression. With progression of CKD, production of 1,25(OH) vitamin D_3 decreases resulting in hypocalcemia. Loss of GFR also leads to decrease in renal phosphorus excretion resulting in high levels. Hypocalcemia, hyperphosphatemia and decreased 1,25(OH) vitamin D_3 stimulate parathormone (PTH) secretion, which increases bone turnover resulting in renal osteodystrophy.

Management of metabolic bone disease in CKD includes dietary restriction of phosphorus, use of phosphate binders, and supplementation with vitamin D and calcium. In the setting of hyperphosphatemia, patients should be instructed to restrict dietary intake of phosphorus. However, dietary phosphorous restriction is a limited strategy as phosphorous is present in most high-quality protein foods and overzealous restriction can lead to protein malnutrition. As a result, phosphate binders given with meals to bind phosphorus in the food so as to increase its elimination via the gastrointestinal tract are often required. Calcium-based phosphate binders such as calcium carbonate are commonly used for both dietary calcium supplementation and for phosphate binding, but can cause hypercalcemia and vascular calcifications when used in excessively large amounts. Calcium-free binders such as sevelamer are an option when additional calcium is not desired. Patients deficient in inactive vitamin D should receive supplementation. Active analogs are used if secondary hyperparathyroidism persists after correction of inactive vitamin D deficiency; adjustment of therapy is guided by PTH target levels that vary based on CKD stage. Oversuppression of PTH is to be avoided as a low bone turnover state may result and lead to adynamic bone disease **(Table 3)**.

Growth Impairment

Growth impairment is a common complication of CKD, and is associated with increased morbidity, mortality and lower health-related quality of life. Growth impairment is multifactorial and is more severe with younger onset of CKD given that infancy and early childhood are periods of very rapid growth. Inadequate nutrition resulting from anorexia and nausea/emesis secondary to uremia contributes in large part to growth failure. Additionally, CKD is a state of growth hormone (GH) resistance, with normal or elevated GH levels but decreased receptors and impaired signaling. Bioavailability of insulin-like growth factor-I is also decreased.

Caloric intake should be optimized, through use of oral or enteral nutritional supplements. Electrolyte abnormalities, including hyponatremia, acidosis and derangement in calcium/phosphorus, may contribute to poor growth and should be corrected. If poor linear growth persists, recombinant human GH is administered subcutaneously at doses to overcome the resistance to GH and aid in attainment of a more normal adult height.

Hypertension

Hypertension, of multifactorial etiology, is extremely common in children with CKD. Contributors include activation of the renin-angiotensin-aldosterone system, sodium retention and fluid overload, hyperactivity of the sympathetic nervous system, and iatrogenic hypertension resulting from medications, such as corticosteroids which are often used in CKD. Treatment of hypertension is of paramount importance and is initiated when blood pressure is consistently above the 90th percentile for age, sex and height. The goal of therapy is to lower blood pressure consistently to 50–75th percentile unless there are signs or symptoms of hypotension.

Pharmacological therapy is guided by the underlying etiology of hypertension. Diuretics, along with salt and fluid restriction, are appropriate for those with fluid overload. Patients with CAKUT may actually have a salt wasting nephropathy, where diuretics are not appropriate. Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers have renoprotective and antiproteinuric effects and are considered first-line agents when there is no contraindication to their use, with monitoring for decrease in GFR and hyperkalemia. Many patients require multiple pharmacologic agents for adequate blood pressure control.

Electrolyte Disorders

Metabolic acidosis and hyperkalemia are important electrolyte abnormalities in patients with CKD. Metabolic acidosis is one of the earliest electrolyte derangements that develops when the GFR falls below 50% of normal. Metabolic acidosis is secondary to decreased ammonia production, low titratable acid excretion and reduced bicarbonate reabsorption. Chronic acidosis is associated with bone demineralization and increased protein degradation. Acidosis is managed with bicarbonate supplementation to maintain a serum bicarbonate concentration greater than or equal to 22 mEq/L.

Hyperkalemia is a problem for patients with severe CKD since distal tubular secretion of potassium remains intact in early CKD. It may be seen earlier in patients with distal renal tubular resistance to aldosterone, such as patients with obstructive uropathy, in patients with sudden decrease in effective circulating volume or increase in potassium load, or following therapy with ACE inhibitors. Management includes dietary restriction of potassium, correction of acidosis and use of sodium polystyrene sulfonate (orally, rectally or mixed with meals) to increase its gastrointestinal elimination.

Table 3 The kidney disease outcomes quality initiative (KDOQI) guidelines: bone metabolism and disease in children with chronic kidney disease (CKD)

Stage	iPTH (pg/mL)	Calcium (mg/dL)	Phosphorus (mg/dL)	Alkaline phosphatase (IU/L)
2	Normal	Normal for age: 0–3 months: 8.8–11.3	Normal for age: 0–3 months: 4.8–7.4	Normal for age: 0–3 months: 100–300
3	35–70	1–5 year: 9.4–10.8 6–12 year: 9.4–10.3	1–5 year: 4.5–6.5 6–12 year: 3.6–5.8	1–5 year: 100–350 6–12 year: 60–450
4	70–110	13 year–adult: 8.8–10.2	13 year–adult: 2.7–4.6	13 year–adult: 40–180
5	200–300	8.8–9.7	1–12 year: 4–6 > 12 year: 3.5–5.5	

Abbreviation: PTH, parathormone.

PREVENTION

Early diagnosis of CKD and management of its complications are critical in delaying or preventing progression to ESRD. While some factors influencing the progression of CKD are not modifiable, those factors that are should be addressed early. Nonmodifiable risk factors for disease progression include the underlying cause of CKD, with acquired glomerular diseases leading to more rapid CKD progression compared to CAKUT. Other nonmodifiable risk factors include more advanced CKD stage, African-American ethnicity and puberty. Hypertension is an important modifiable risk factor. Control of hypertension is shown to reduce the rate of decline of GFR in adults and children. Proteinuria is another modifiable risk factor for progression. Antagonists of the renin angiotensin system are beneficial in patients with CKD, both for their antihypertensive and antiproteinuric effects, and are key agents in slowing disease progression. Other factors which may also affect disease progression and should be addressed include the aforementioned complications of CKD: metabolic acidosis, dyslipidemia, altered calcium phosphate metabolism and anemia.

OUTCOME

Data from a large cohort of children with CKD in Italy showed that nearly 70% of the cohort progressed to ESRD by the age of 20 years. The outcome for children who have progressed to ESRD depends largely on whether renal replacement therapy is readily available, with rates of renal replacement therapy and kidney transplantation being generally low in developing countries. Renal transplantation is the preferred treatment for ESRD when possible, as it offers advantages over dialysis both in regards to survival as well as quality of life. When renal transplantation is not possible or while patients are awaiting transplantation, either peritoneal dialysis or hemodialysis may be used as the form of renal replacement therapy.

IN A NUTSHELL

1. Children with CKD are asymptomatic until they progress to advanced CKD making early diagnosis and intervention challenging yet imperative.
2. There are several estimating equations for children with CKD which can help categorize stages of CKD in those above the age of 2 years.
3. Congenital structural anomalies of the kidney and urinary tract are the most common cause of CKD in children.
4. Careful monitoring is required to manage complications of CKD namely: anemia, growth impairment, mineral and bone disorders, hypertension and electrolyte abnormalities.
5. Treatment of hypertension and proteinuria can slow the decline of renal function.
6. Renal transplantation is the treatment of choice in children with ESRD.

MORE ON THIS TOPIC

Gulati S, Mittal S, Sharma RK, Gupta A. Etiology and outcome of chronic renal failure in Indian children. Pediatr Nephrol. 1999;13:594-6.

Hari P, Singla IK, Mantan M, et al. Chronic renal failure in children. Indian Pediatr. 2003;40:1035-42.

Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. Pediatrics. 2003;111:1416-21.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. Kidney Int suppl. 2013;3:1-150.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;76 (suppl 113):S1-S130.

Chapter 41.22
End-Stage Renal Disease
Kirtida Mistry, Asha Moudgil

CHRONIC DIALYSIS

End-stage renal disease (ESRD) is the most advanced stage of chronic kidney disease (CKD) when glomerular filtration rate (GFR) is less than 15 mL/min/1.73 m^2. Irrespective of etiology, all ESRD patients eventually develop symptoms and signs of uremia. Once ESRD develops, lifesaving renal replacement therapy (RRT) in the form of either dialysis or renal transplantation is required. The indications for initiating dialysis are listed in **Box 1**.

Dialysis refers to the movement of solutes across a semipermeable membrane, resulting in removal of waste products or uremic toxins and correction of electrolyte disturbances. Additionally, dialysis provides the capability for fluid removal or ultrafiltration. Two forms of chronic dialysis modalities are available for management of ESRD: hemodialysis (HD) and peritoneal dialysis (PD). In general, HD is performed by skilled staff in a dialysis unit, whereas PD is a form of home therapy. There is a growing pediatric population in more developed countries performing home HD. These tend to be patients without psychosocial contraindications to home dialysis, but in whom for various medical reasons PD is not an option. The factors determining the choice of dialysis modality are listed in **Table 1**. Worldwide, PD has been the predominant modality used in children, but the proportion of patients on maintenance HD is rising. All chronic dialysis patients, irrespective of modality, require meticulous medical management of the complications of ESRD (Chapter 41.21).

BOX 1 **Indications for initiation of chronic dialysis**

- Estimated GFR less than 15 mL/min/1.73 m^2
- Estimated GFR greater than 15 mL/min/1.73 m^2 with any of the following:
  - Fluid overload including: (i) worsening edema due to oliguric renal failure; (ii) pulmonary edema; (iii) congestive heart failure; (iv) hypertension due to fluid overload
  - Uncontrolled hyperkalemia, metabolic acidosis or hyperphosphatemia
  - Symptoms and signs of uremia
  - Inability to maintain adequate nutrition
  - Poor growth and development.

Table 1 Factors determining the choice of chronic dialysis modality

Medical
• Ability to obtain vascular access
• Integrity of the peritoneal membrane
• Presence of comorbidities
• Patient's age and size
• Expertise of staff and availability of equipment

Psychosocial
• Patient and family adherence
• Family and social support structure
• Psychiatric illness in patients and/or caregivers
• *Living circumstances:* Presence of hygienic space for home dialysis
• Parental or caregiver preference
• Economic factors

Chronic Peritoneal Dialysis

Peritoneal dialysis utilizes the patient's peritoneal surface as the semipermeable membrane for solute clearance and ultrafiltration. The process involves instillation of sterile biocompatible fluid (dialysate) into the abdominal cavity via a cuffed PD catheter **(Fig. 1)**. The fluid dwells in the peritoneal cavity for a period of time allowing for solute and water exchange to occur and is subsequently drained by gravity and discarded (PD effluent). Solute clearance occurs primarily by simple diffusion from high to low concentration, whereas ultrafiltration is achieved by establishing an osmotic gradient using dialysate with varying dextrose concentrations. The therapy is performed daily.

Contraindications to PD are listed in **Table 2**. There are essentially two forms of chronic PD: (1) continuous ambulatory PD (CAPD) and (2) automated PD (APD). The former does not require a cycler and requires fewer consumables and thus is more affordable and accessible for patients in less developed countries. Exchanges are performed manually during the day and the patient has a prolonged overnight dwell. APD involves an automated cycling device that performs the prescribed therapy, usually when the patient is asleep. **Table 3** lists the complications of PD.

Chronic Hemodialysis

Hemodialysis is a form of dialysis where access is required to the patient's bloodstream, either via a central venous HD catheter or
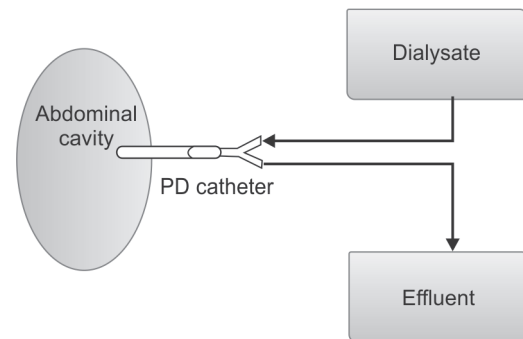
Figure 1 Peritoneal dialysis. A biocompatible and sterile fluid called dialysate is instilled into the peritoneal cavity via a dialysis catheter. It dwells there for a prescribed period of time allowing for solute and water exchange to occur, and subsequently drains out and is discarded (effluent). The arrows depict the direction of fluid flow

Table 2 Contraindications to chronic peritoneal dialysis

Absolute contraindications
• Omphalocele or gastroschisis
• Bladder exstrophy
• Irreparable abdominal hernias, diaphragmatic hernia or pleuroperitoneal fistula
• Peritoneal membrane failure, sclerosis or excessive adhesions limiting dialysate flow
• Lack of competent caregiver to perform dialysis in a child

Relative contraindications
• Nonadherence to medical therapy
• Lack of living conditions conducive for performing home dialysis
• Impending abdominal surgery
• Inflammatory or ischemic bowel disease
• Imminent kidney transplant
• Abdominal wall or skin infections
• Morbid obesity
• Severe malnutrition
• Peritoneal leaks

Table 3 Complications of dialysis

Peritoneal dialysis
• *Infection:* Peritonitis, exit site and tunnel infections • Abdominal wall hernias; peritoneal fluid leaks; hydrothorax • Pain • Hemoperitoneum • Malnutrition due to protein loss and emesis • Hyponatremia • Peritoneal dialysis catheter occlusion, migration or displacement
Hemodialysis
• Hypotension or hypertension • Muscle cramps, headache, nausea and emesis • Dialysis disequilibrium syndrome, most commonly during the first few treatments • Pruritus • Iron deficiency anemia, hemolysis • *Access related complications:* Infection, thrombosis and malfunction • Hypoxemia, cardiac arrhythmias and chest pain • Air embolus

a surgically created arteriovenous fistula or graft. The principle of solute clearance primarily by diffusion is identical to that in chronic PD, while ultrafiltration occurs by a hydrostatic pressure gradient created across the dialyzer membrane by the HD machine **(Fig. 2)**. HD treatments are usually performed at least three times per week, although evidence is mounting for improved outcomes and quality of life with more frequent dialysis. A water purification system is required for HD so as to minimize patient exposure to chemical and infectious contaminants. Chronic HD results in relatively more hemodynamic instability and risk of blood loss, and is hence more challenging to perform in infants and small children, than PD. Complications of chronic HD are listed in **Table 3**.

Outcomes of Pediatric Chronic Dialysis
When children develop ESRD, mortality is increased by 30-fold compared to their peers without ESRD. Prognosis of ESRD has improved significantly over the past decades due to ready access to chronic dialysis. Despite this, the overall mortality of children with ESRD is about 4% in the United States, being highest in the youngest children. Compared with patients on dialysis, renal transplant is associated with four-fold lower mortality.
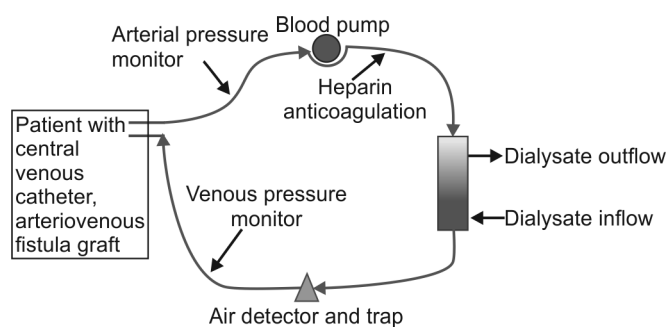
Figure 2 Schematic of hemodialysis circuit. Hemodialysis requires access to the patient's blood stream, by either a central venous double lumen catheter or using a surgically created arteriovenous fistula or graft. The arrows depict the direction of blood and dialysate flow. Blood is pumped out of the patient via the access line and enters the dialyzer. The tubing through which the blood flows in the dialyzer is bathed in dialysate, and this is the site of solute exchange and water removal. Blood exiting the dialyzer is free of uremic toxins and is returned to the patient via the return line. Monitoring systems are built into the circuit for monitoring and patient's safety

RENAL TRANSPLANTATION
Compared to dialysis, transplantation is associated with lower morbidity and improved growth and nutrition, school performance and quality of life. Preemptive transplant from a living donor can help bypass dialysis and is cost-saving. Children are ideal candidates for transplantation due to lack of co-morbidities. Contraindications to transplant are listed in **Table 4**.

Recipient Evaluation
Extensive work-up and health optimization is needed for a child prior to transplantation. Determining the cause for ESRD helps plan management for diseases with potential for recurrence [focal segmental glomerulosclerosis, atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis (GN)]. The urinary bladder is evaluated by postvoid ultrasonography, voiding cystourethrogram and, if required, by urodynamic studies. Appropriate reconstruction surgeries such as bladder augmentation may be required prior to transplantation. Bilateral nephrectomy is indicated in children with chronically infected or large polycystic kidneys, severe nephrotic syndrome, intractable hypertension, nephrolithiasis or polyuria. Children should be screened for infections including tuberculosis, human immunodeficiency virus (HIV), hepatitis B and C, cytomegalovirus, Epstein-Barr virus and varicella, and receive age appropriate immunizations.

The donor and the recipients should be blood group compatible as incompatibility results in hyperacute rejection. Genetic differences between individuals are recognized by dissimilarities in the major histocompatibility complex human leukocyte antigens (HLA) antigens of class I and class II. HLA mismatches between the donor and the recipient determine the strength of immunologic response and potential for development of detrimental de novo donor specific anti-HLA antibodies after transplant. Recipients are tested for anti-HLA antibodies to determine their sensitization to HLA antigens, which can occur in response to blood transfusions or previous transplant. These antibodies preclude transplant from donors carrying these specific HLA molecules. Additionally, each recipient is cross-matched with the prospective donor to ensure absence of anti-HLA antibodies to their specific donor.

The family's inability to comply with medical therapy should be addressed prior to transplant as nonadherence is the most important cause of graft failure, particularly in adolescents. Some children need cardiac, pulmonary and other evaluations. Growth and nutrition should be optimized as malnutrition and obesity pose risks following transplantation.

Donor Source and Evaluation
Donors can be living-related, unrelated or altruistic. Their work-up includes a thorough medical history, physical examination,

Table 4 Contraindications to transplantation

Absolute
• Acute infection • Recent untreated malignancy (need to wait 2–5 years) • Progressive neurologic disease; persistent vegetative state • Multiorgan failure
Relative*
• HIV infection (can be controlled with medications) • Hepatitis B and C infection (can be controlled with antiviral medications) • Nonadherence with medical therapy (counseling)

*Transplantation can be undertaken after addressing these issues.
Abbreviation: HIV, human immunodeficiency virus

blood group and HLA typing, liver and kidney function tests including urinalysis and 24 hours urine protein analysis, screening for infections (HIV, hepatitis B and C, syphilis and tuberculosis) and age appropriate malignancies and cardiac evaluation. Renal anatomy is defined by ultrasonography and renal vascular anatomy by contrast angiography by spiral CT or MRI.

Allografts from living (related/unrelated) donors have a longer half-life compared to those from deceased donors. This is attributed to healthier organs, avoidance of graft injury during dying process and minimization of cold ischemia time. Injury due to death, ischemia and reperfusion increase the risk of acute rejection. Compatible blood group and a negative cross-match are desired for a successful transplant. While HLA matching is not required, HLA identical grafts have a longer half-life compared to less well-matched grafts. The practice of *transplant tourism* involving purchase of organs from unknown living donors is condemned by the *Transplant Societies in the Declaration of Istanbul.*

Procedure

Donor nephrectomy is done by open or by laparoscopic procedure. Depending upon recipient size, the allograft is placed either in the iliac fossa or higher up in the retroperitoneum and the donor artery and vein are connected to the recipient's iliac vessels or aorta and inferior vena cava. The ureter is anastomosed to the bladder, or rarely to the native ureter or urinary conduit. Intraoperatively, liberal amount of intravenous (IV) fluids are given and central venous pressure maintained between 10 cm and 15 cm H_2O to maintain perfusion to the transplanted organ. Postoperatively, adequate fluid and electrolyte management and proper blood pressure support is important to ensure adequate allograft perfusion to optimize graft function. Immunosuppression is most potent at the onset and becomes less intense afterwards. Induction therapies used at transplant include either polyclonal (thymoglobulin) or monoclonal (anti-IL2 receptor) antibodies with high dose methylprednisolone; the choice of induction depends upon the immunologic risk of the recipient. Maintenance immunosuppression uses a combination of a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative drug (mycophenolate mofetil or azathioprine) and tapering doses of prednisolone. Children should be monitored for postoperative complications, graft function, side-effects of immunosuppressive and other medications and need ongoing management of CKD to ensure long-term success of transplant.

Complications and Outcome

Delayed graft function due to acute tubular necrosis may occur due to hypotension in the donor or recipient and is common in organs from deceased donors, particularly those with prolonged cold and warm ischemia time. Acute rejection in the first few months has become uncommon due to use of potent immunosuppression. Its occurrence after many months is usually related to nonadherence with medications. Acute rejection is suspected when there is sudden increase in serum creatinine, decrease in urine output, fever, graft tenderness, increase in blood pressure and proteinuria; the diagnosis is confirmed on renal biopsy. Patients on potent immunosuppression are also at risk of opportunistic or community acquired viral and bacterial infections. They need to be screened for side effects of medications, and steps taken to ensure growth and nutrition, and bone and cardiovascular health.

IN A NUTSHELL

1. End-stage renal disease refers to the most advanced form of CKD when GFR is less than 15 mL/min/1.73 m^2. ESRD presents with uremic complications involving multiple organ systems, and requires institution of RRT in the form of HD, PD or renal transplantation.
2. Renal transplantation is associated with reduced risk of mortality and morbidity and improved quality of life compared to chronic dialysis.
3. Acute rejection is the most common complication following transplantation, noted usually in the first 3 months, but may occur later with nonadherence to immunosuppression.
4. Optimal long-term management of transplant recipients involves minimizing immunosuppression without risking rejection, blood pressure control, maintain nutrition, growth and optimize quality of life, and screen for infections, dyslipidemia, hyperglycemia, proteinuria and malignancies.

MORE ON THIS TOPIC

Abuali MM, Arnon R, Posada R. An update on immunizations before and after transplantation in the pediatric solid organ transplant recipient. Pediatr Transplant. 2011;15:770-7.

Barsoum RS. Overview: end-stage renal disease in the developing world. Artif Organs. 2002;9:737-46.

Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24:1633-42.

Gebel HM, Liwski RS, Bray RA. Technical aspects of HLA antibody testing. Cur Opin Organ Transplant. 2013;18:455-62.

Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351:2715-29.

Hari P, Singla IK, Mantan M, et al. Chronic renal failure in children. Indian Pediatr. 2003;40:1035-42.

Harshman LA, Neuberger ML, Brophy PD. Chronic hemodialysis in pediatric patients: technical and practical aspects of use. Minerva Pediatr. 2012;64:159-69.

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl 3):S1-155.

Moudgil A, Puliyanda D. Induction therapy in pediatric renal transplant recipients: an overview. Paediatr Drugs. 2007;9:323-41.

Schaefer F, Warady BA. Peritoneal dialysis in children with end-stage renal disease. Nat Rev Nephrol. 2011;7:659-68.

Solez K, Racusen LC. The Banff classification revisited. Kidney Int. 2013;83:201-6.

Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012;93:1-10.

Section 42 NEUROLOGICAL DISORDERS

Section Editors Satinder Aneja, Suvasini Sharma

Chapter 42.1
Approach to Neurological Disorders
Suvasini Sharma, Satinder Aneja

A comprehensive neurological evaluation which includes a detailed history, physical examination and the judicious use of investigations is the key to reach the diagnosis in children with neurological problems. A plethora of investigations such as MRI, CT, EEG, electrophysiological studies, metabolic testing, etc. are available; however, the use of these should be guided by clinical judgment and the likely etiological possibilities. In this chapter, the general clinical approach to a child with neurological problems is discussed. In the following chapters, the use of various investigations which are useful in pediatric neurology will be covered. The subsequent chapters will cover the various diseases of the central nervous system.

NEUROLOGICAL HISTORY

For reaching a neurological diagnosis, the one most important prerequisite is a thorough history. History should be obtained from the parents (especially the mother), the child (if older than 3 years of age), and other caregivers (e.g., grandparents). The affected child must always be given the opportunity to describe his symptoms. If the child participates actively, the child's level of understanding and description of his symptoms help the physician to make a judgment of the child's intellectual level and language skills.

The history should begin with the details of how information was obtained, demographic details and handedness for children older than 3 years of age. History should detail all presenting complaints in sufficient detail. Every symptom should be carefully analyzed by asking the patient/parents relevant questions. The common symptoms in neurological diseases include headache, seizures, weakness, pain, vision and hearing problems, squint, stiffness or limpness or limbs, sensory abnormalities, bladder and bowel problems. Relevant non-neurological symptoms must also be enquired about. For example, in a child with dystonia and rigidity, the presence of jaundice indicates Wilson's disease as a likely possibility. In a patient with chorea, the presence of arthritis and photosensitive rash points to systemic lupus erythematosus as a likely possibility.

A large subset of children present with developmental delay, deviant development, or regression. Diseases affecting the child's brain must be understood in the developmental context. The antenatal and perinatal history must include the details of the pregnancy, labor, status at birth, need for resuscitation, lethargy, seizures, neonatal intensive care unit (NICU) stay, jaundice, etc. In case of home delivery the details are ascertained from mother and other family members as records are often not available. A

sole history of delayed cry is not enough to attribute the etiology to perinatal asphyxia. The physician must enquire whether the child had any features of neonatal encephalopathy, i.e., lethargy, feeding difficulties, seizures, etc. along with the history of delayed cry.

The developmental history is a very important part of the neurological evaluation. The achieved milestones in various domains—gross motor/fine motor/language/social must be elicited. It is helpful to start with the most recent milestones as the recall is better. The physician should determine whether the delay is global (all domains) or pure motor (e.g., neuromuscular)/language (e.g., deafness)/social (e.g., autism). Any dissociation in the various spheres of development must be looked for. The parents should also be asked about the vision and hearing function. Behavior problems such as hyperactivity, aggressive behavior and communication difficulties must also be asked about. In the school going child, the child's academic performance and any recent worsening also needs to be asked about. The latter could be an early sign of a neurodegenerative disorder.

The past history is important because neurologic symptoms may be related to systemic diseases. A three-generation family history and pedigree charting helps to understand and know about possible hereditary disorders. In the Indian context history of contact with tuberculosis would be relevant in practically all children. Depending on the presentation relevant family history could include history of epilepsy, sibling deaths, muscular dystrophy, degenerative disorders, migraine, early cardiac deaths or cerebrovascular disease, etc. The questions that need to be answered by history are discussed here:

Q1. At What Age did the Problem Start?
Early onset problems are likely to be due to perinatal insult, intrauterine problems and brain malformations. Infective, metabolic/degenerative and vascular processes can occur in any age group, but the manifestations will vary according to the age at presentation. Establish that the child was normal prior to the disease onset by means of the developmental history, school performance and past history.

Q2. How did the Symptoms Start; i.e., How was the Onset—Acute, Subacute or Insidious?
Acute onset implies an onset within a few hours or days. Acute onset disorders are likely to be of infective, parainfectious, vascular, or traumatic etiology. Insidious and chronic onset means the problem has been there for months to years. Often the parent cannot exactly remember when the problem started exactly. Chronic onset problems are more likely to be degenerative.

Q3. What Parts of the Neuroaxis are Involved?
Establish what parts of the neuroaxis are involved. Decide whether the process is diffuse, focal or multifocal. The presence of seizures, aphasia, cognitive decline and behavioral problems indicate involvement of the cerebral cortex. Altered sensorium or impaired consciousness indicates involvement of the reticular

activating system. The presence of cranial nerve deficits indicates involvement of the brainstem or the supranuclear pathways. Focal neurological deficits are likely due to vascular pathology such as stroke or space occupying lesions such as tumors. In patients with neurodegenerative disorders, white matter disorders (e.g., leukodystrophies) are characterized by early onset of spasticity, and motor regression while cognitive decline and seizures occur late in the course of illness. In gray matter neurodegenerative disorders (e.g., neuronal ceroid lipofuscinosis), cognitive decline and seizures occur early, and motor function is affected late in the course of illness. Basal ganglia disorders (e.g., Wilson's disease) are characterized by rigidity, dystonia, and involuntary movements such as tremors and choreoathetosis. Cerebellar disorders are characterized by the presence of ataxia, hypotonia and intention tremors.

Q4. Is the Disease Process Static, Progressive or Intermittent?

Static processes imply a onetime insult, e.g., perinatal asphyxia, traumatic brain injury, or meningoencephalitis. After the insult, the patient may improve, or remain at the same level, but there is no worsening. In progressive disorders, the symptoms continue to worsen with time. The likely etiology is degenerative and metabolic disorders; rarely this may be the presentation with slowly growing neoplastic lesions and toxin exposure. In intermittent disease presentations, the child is well in-between the episodes. Examples include paroxysmal disorders such as epilepsy and migraine.

EXAMINATION

The neurological examination has to be tailored to patient's condition, age, setting (OPD/ward/Casualty/ICU). It is neither *necessary* nor *possible* to do all aspects of neurological examination in all children. For example, in a child who has presented with a history of seizures, a detailed sensory testing will only tire the patient, and not add to any useful information.

The traditional neurological examination can be done in older children and adolescents, however, the scheme and detail of examination needs to be modified for infants and young children. The sequence of examination should be flexible and should be determined by the child's mood and comfort level. It is beyond the scope of this chapter to cover all aspects of the traditional neurological examination (The reader is referred to the appropriate sources at the end of this chapter). The schema for neurological examination of the older child is given in **Box 1**. Basic aspects of the neurological examination of the older child and some techniques of neurological examination of children less than 2 years of age will be discussed. The results of the neurological examination need to be interpreted in the developmental context of the child's maturing nervous system.

General Physical Examination

Features of facial dysmorphism and neurocutaneous stigmata must be looked for. Neurocutaneous markers include café au lait spots, ash leaf macules, neurofibromas, Lisch nodules in the iris, patterned skin nevi (e.g., whorled lesions in hypo-melanosis of Ito), and hemangiomas. Coarse facies are seen in mucopolysaccharidosis, GM1 gangliosidosis and mucolipidosis. Hair abnormalities must also be looked for—in Menkes disease, the hair is sparse, hypopigmented and kinky. Eye examination must be done to look for cataracts (galactosemia), Kayser-Fleischer rings (Wilson disease) and telangiectasia (ataxia telangiectasia).

BOX 1 Schema of neurological examination in older children/adolescents

- *Higher mental functions*
  - Level of consciousness
  - General behavior and appearance
  - Orientation
  - Attention span
  - Speech and language
  - Memory
  - Higher cognitive functions
  - Release reflexes
- *Cranial nerve examination (I to XII)*
- *Motor examination*
  - Bulk
  - Tone
  - Power
  - Deep tendon reflexes
  - Superficial reflexes
  - Abnormal movements
  - Gait
- *Sensory testing*
  - Touch
  - Pain
  - Temperature
  - Joint position sense
  - Vibration
  - Romberg's sign
  - Cortical sensation tests
- *Cerebellar signs*
- *Meningeal signs*
- *Examination of the autonomic nervous system*

Examination of the Head and Spine

Any skull defects must be looked for. The sutures must be palpated for any ridging or sutural diastasis. The head circumference should be measured and interpreted as normal, *microcephaly* (< –3SD below the median), or *macrocephaly* (> 2SD above). Careful examination of the head may help to differentiate primary from secondary (acquired) microcephaly. Macrocephaly may occur due to hydrocephalus, rickets, megalencephaly, subdural effusions and intracranial tumors. Children with hydrocephalus often have sun-setting sign in their eyes and distended scalp veins.

The shape and symmetry of the head must be observed for any abnormalities. Many young infants may have *plagiocephaly* because of positional asymmetry. *Craniosynostosis* occurs because of premature closure of the sutures and results in abnormally shaped head. Premature closure of the coronal suture prevents growth of the skull in the anteroposterior direction, and leads to a flattened appearing head called brachycephaly. Closure of the sagittal suture prevents growth in the lateral direction, resulting in a long narrow skull, called dolichocephaly.

The spine must be examined in all children with neurological illness, but this is especially important in children with paraplegia. A tuft of hair or dimple may indicate an underlying neural tune defect. Any localized vertebral tenderness must be looked for. The spinous processes must be felt, any kyphosis, lordosis, or scoliosis looked for. Lumbar lordosis is common in neuromuscular disorders such as Duchenne muscular dystrophy. Scoliosis may be seen in children with Duchenne muscular dystrophy, Friedrichs ataxia and cerebral palsy.

Systemic Examination

Systemic examination may provide important clues to the etiology. In a patient with chorea, the presence of a heart murmur may point to rheumatic heart disease. A child with stroke may

have an underlying congenital heart disease. A child with neurodegenerative disorder may have hepatosplenomegaly which points towards the possibility of lysosomal storage disease.

Neurological Examination: Observation

Much can be learned by simply observing the child unobtrusively during the history-taking procedure. The co-ordination of the child can be assessed. Movement disorders such as tics, tremor, choreoathetosis may also be noted. The gait should be noted as the child enters the room or walks about the room. This part of the examination also provides an opportunity to assess the child's behavior. Hyperactivity, impulsivity and easy distractibility may be noted. The mother-child interaction may also be observed at this time.

Higher mental functions Disorders of consciousness and examination of the unconscious child are detailed in a subsequent chapter. In the conscious child, testing for orientation, attention span, language, memory and higher cognitive abilities are performed depending on the age and presenting complaints of the child.

Cranial Nerve Examination

The olfactory nerve rarely requires testing in routine clinical practice. Testing of optic nerve involves the following components: visual acuity, color vision, field of vision, fundus and pupillary reactions. The visual acuity in various age groups is: at birth—20/2,000, 2 months of age—20/200, 1 year—20/60, 4 years—20/40; It reaches adult range by 5 years. Test charts include Snellen chart for distant vision and near card (Rosenbaum pocket vision screener held at 14 inches) for near vision. Visual fields are clinically tested by the confrontation test. Field defects are said to be homonymous if the same part of the field is affected in eyes, e.g., a right homonymous hemianopia means there is a field defect in the temporal field of the right eye and nasal field of the left eye. Whereas a bitemporal hemianopia would be a heteronymous field defect. Homonymous field defects are called congruous, if the field defects in both eyes match exactly or incongruous if the field defects do not match exactly.

Evaluation of the pupillary light reflex is critical in patients with coma, head injuries, stroke and brain tumors.

The third, fourth and sixth cranial nerves control the movements of upper eyelid, eyeball and pupils. They help in finding, fixating, focusing and following a visual target. These three nerves are tested together. The movements of both eyes, when they move together are known as *conjugate* movements. The conjugate movements are controlled by centers in the frontal lobe and brainstem (pons and midbrain). Any lesions in these regions lead to supranuclear gaze palsies. The medial and lateral recti have only the primary actions of adduction and abduction respectively. However, the other muscles (superior and inferior recti, and superior and inferior obliques) have multiple actions, because of their oblique attachments on the eyeball and consequent direction of pull. The superior rectus elevates (primary action) and adducts (secondary action). Hence, to test the pure elevation action of the superior rectus, the patient is first asked to abduct his eye (so that the secondary adduction action is counteracted) and then elevate. In the abducted position, superior and inferior recti act as pure elevators and depressors respectively. Similarly, in the adducted eye, the superior and inferior obliques act as pure depressors and elevators respectively.

The trigeminal nerve has a motor and a sensory component. The three divisions of V nerve (ophthalmic, maxillary and mandibular) innervate face, teeth, oral and nasal cavities, scalp up to vertex, intracranial dura, cerebral vasculature and proprioceptive inputs from masticatory muscles. The motor component innervates the four masticatory muscles: temporalis, masseter, medial pterygoid and lateral pterygoid. Chewing movements include: jaw protrusion and retraction, opening and closure and side-to-side movement. In addition, testing for the jaw jerk and corneal reflex are part of the trigeminal nerve examination.

The seventh nerve is mainly a motor nerve, supplying all the muscles concerned with facial expression on one side. The sensory component is small (the nervus intermedius of Wrisberg); it conveys taste sensation from the anterior two-thirds of the tongue and, variably, cutaneous sensation from the anterior wall of the external auditory canal. In upper motor neuron lesions, the upper part of the face is spared because of bilateral innervations. In lower motor neuron lesions, there is complete lack of ipsilateral facial movements. Eye closure is impaired, ipsilateral palpebral fissure is widened, ipsilateral nasolabial folds get obliterated and the angle of the mouth deviates towards the opposite unaffected side as patient tries to smile.

The vestibulocochlear nerve has two components, the vestibular and cochlear, blended into a single trunk. The cochlear portion subserves hearing; the vestibular nerve subserves equilibrium, coordination and orientation in space. Examination of the eighth nerve consists of hearing evaluation, tuning fork tests, and caloric testing for the vestibular system.

The glossopharyngeal and the vagus nerves are usually tested together. The pitch and quality of the voice, any nasal twang or pooling of secretions must be looked for. The palatal movements and position of the uvula need to be seen. The gag reflex is uncomfortable and should be done at the end of examination. In infants and young children, a feed can be observed. If the child appears to be swallowing well without any choking or drooling, testing for the gag reflex can be omitted. The afferent limb of the reflex is mediated by CN IX and the efferent limb through cranial nerves IX and X. The reflex center is in the medulla.

The spinal accessory nerve innervates the sternocleidomastoid and trapezius muscles. In unilateral sternocleidomastoid weakness, the child will fail to turn the head against resistance to the opposite side. Unilateral paresis causes little change in the resting position of the head. In bilateral weakness, child may not be able to lift his head off the couch. With trapezius weakness, there is drooping of shoulders with flattening of trapezius ridge.

The hypoglossal nerve supplies the musculature of the tongue. The patient should be asked to open his mouth and the surface, size, shape and position of the tongue should be observed. Look for any fasciculations. Fasciculations are common in anterior horn cell disease such as spinal muscular atrophy. The patient should be asked to protrude the tongue, move it in and out, from side-to-side and upward and downward. In case of unilateral weakness, tongue deviates towards the weak side on protrusion (because of the unopposed action of the normal genioglossus).

Motor Examination

Motor system examination begins with the observation of the muscle bulk. Any atrophy or hypertrophy should be looked for, and any asymmetries. In Duchenne muscular dystrophy, there is prominent hypertrophy of the calf muscles. In neuropathies, there is early atrophy of the extensor digitorum brevis muscle. There is long appearance of the face in some congenital myopathies and myotonic dystrophy.

Tone is defined as resistance to passive stretching. It excludes resistance as a result of joint, ligament, or bone problems. Methods to assess tone are described in **Box 2**. Hypertonia is defined as abnormally increased resistance to externally imposed movement about a joint. It may be caused by spasticity, dystonia, rigidity, or a

BOX 2 Assessment of tone

Assessment of tone

- *Posture:* Posture observe the spontaneous posture of the child when he is lying down in bed. A floppy hypotonic child will lie in a frog-like position. A hypertonic child will have extended lower limbs and may have scissoring.
- *Feel the muscles:* Normal muscles feel firm. Hypotonic muscles feel flabby and soft. Hypertonic muscles feel stiff.
- *Resistance to passive stretching:* Examine this in all four limbs. Especially look for asymmetries. If the tone appears increased, see if this increase is there throughout the range of motion, or there is an initial catch, and later give-way. If the tone is increased throughout the range, it is rigidity. If there is an initial catch, and then the tone reduces, it is spasticity. In spasticity, you will also find that the tone varies with the speed of stretching (velocity dependent). In infants also look for the truncal tone. Young infants with evolving cerebral palsy may have axial hypertonia with limb hypotonia and vice versa.
- *Flappability:* Shake the limb to and fro and observe the movement at the distal joint, e.g., shake the forearm, and observe the movement at the wrist. If there is hypotonia, the movement at the wrist (i.e., flappability) will be increased. If there is hypertonia, the movement at the wrist will be decreased.

Apart from the methods mentioned above, in infants, the range of motion can be quantified using angles as described by the Amiel-Tison method. Also, some maneuvers are useful in demonstrating the hypotonia in floppy infants, e.g., pull to sit, vertical suspension and ventral suspension.

Table 1 Muscle power grading by Medical Research Council (MRC)

Grade	Definition
5	Normal strength
4	Muscle holds the joint against a combination of gravity and resistance
3	Muscle cannot sustain the joint against resistance, but moves the joint fully against gravity
2	Muscle moves the joint when gravity is eliminated
1	A flicker of movement is seen or felt in the muscle
0	No movement

Presence of anti-gravity movements and level of power help in this assessment. Peripheral hypotonia is associated with paralysis (manifest in infants as reduced spontaneous and antigravity movements) and central hypotonia is nonparalytic.

For testing *muscle power*, the patient should be seated comfortably on firm surface and appropriately undressed to allow visualization of the muscle. In bed-bound patients, power grades can be approximated. To test distal muscle, the proximal limb should be stabilized. For grading the muscle power, the most frequently used scale is Medical Research Council scale **(Table 1)**. This is based on gravity resistance techniques.

The *deep tendon reflexes*, also known as muscle stretch reflexes, are tested next. When a normal muscle is passively stretched, its fibers resist the stretch by contracting. In the monosynaptic stretch reflex, sudden lengthening stretches the muscle spindles, which send impulses via the primary spindle afferents into the spinal cord. The spindle afferents synapse directly on the alpha motor neurons, innervating the muscle, causing a reflex contraction of the muscle. The patient should be comfortable, relaxed and properly positioned. The muscle should be exposed. The hammer strike should be quick, crisp and forceful (as necessary). It is important to look for the muscle contraction, not just the movement at the joint. The optimal position is usually midway between ranges of motion. The adequate stimulus must be delivered at the proper spot. Reinforcement techniques, such as the Jendrassik maneuver can be used if the reflexes are not elicitable. The commonly tested deep tendon reflexes in clinical practice include the knee jerk, the ankle jerk, the biceps, the triceps and the supinator reflexes. Excessively brisk reflexes occur with upper motor neuron lesions. Remember however that such reflexes may also occur with fright, agitation and anxiety. Hence, brisk reflexes are of pathological significance only if taken in conjunction with features of upper motor neuron disease such as spasticity and extensor plantar responses. Reflexes may be absent or reduced in lower motor neuron lesions, peripheral neuropathy. Reflexes may also be absent in the *spinal shock* phase after spinal injury or acute transverse myelitis. An extensor plantar response often appears long before the reflexes return.

In young infants, the predominant flexor tone of early infancy almost invariably suppresses the triceps jerk entirely, and the ankle jerk may be difficult to elicit. Young children are often relatively hypotonic and their reflexes may be depressed by adult standards.

The superficial reflexes which are tested include the corneal reflex, the abdominal reflexes, the plantar responses, the cremasteric reflex and the anal reflex. An extensor plantar response indicates disturbance in the upper motor neuron system. However, the plantar response is normally extensor in infants under 1 year of age.

Finally, the gait of the patient should be observed. The patient should be observed walking, back and forth normally in a corridor and turning right and left. The patient should also be asked to walk

combination of these. *Spasticity* is a velocity-dependent resistance of a muscle to stretch. In spasticity, if the passive movement is made slowly, there may be little resistance. If however, the movement is made quickly, there may be an initial increased resistance followed by a *catch*. Spasticity can vary depending on a child's state of alertness, activity, or posture. Spasticity can be increased by anxiety, emotional state, pain, surface contact, or other nonnoxious sensory input. Spasticity is caused by lesions in the corticospinal pathways (the pyramidal system). *Rigidity* is a diffuse increase in resistance to passive stretching that occurs primarily with lesions that involve the basal ganglia (the extrapyramidal system). The increased tone affects both agonist and antagonist muscles and is equally present throughout the range of motion at a given joint. The increased tone is constant from beginning to the end of the movement and does not vary with the speed of the movement. *Dystonia* is used to describe spontaneous, involuntary, sustained muscle contractions that force the affected part of the body into abnormal twisted movements or postures, sometimes with co-contraction of agonists and antagonists. Dystonia occurs because of disturbance in the extrapyramidal system.

Tone can be markedly influenced by sleep, drugs, stress, excitement or systemic illness. The resting tone changes during early infancy. The flexed tone and posture of the newborn gradually decreases until normal mature tone is seen by about the age of 6 months.

In addition to appendicular tone, the axial tone in the infant is tested by supporting the trunk in supine, prone, vertical suspension and ventral suspension and observing the position of the infant. The examiner also observes the head and trunk posture and movement when the infant is held in an upright sitting position. These maneuvers and the traction response assess active tone (power) as well as tone. Hypotonia can be associated with dysfunction of both central and peripheral nervous system or musculoskeletal system. An attempt should be made to determine however whether the hypotonia is central (related to central nervous system pathology) or peripheral (related to peripheral nervous system) or both.

on his toes and heels, hop and tandem walk. The child is observed for type of gait (e.g., wide based or narrow) and also for associated movements of arms and any asymmetry.

Sensory Examination

Sensory system examination requires a lot of cooperation from the patient. There is a lot of subjectivity in this testing. Detailed sensory testing is not needed in each and every patient. It is needed in searching for a level of lesion in a child with suspected spinal cord disease, patient with suspected syringomyelia, or in delineating a peripheral nerve or plexus lesion. One should explain to the patient about the procedure and should take the patient into confidence. The test should be demonstrated to him/her with eyes open. Then patient should be requested to close his/her eyes during the actual testing.

Two ascending tracts are important components of sensory system. These are the spinothalamic tract (pain, light touch and temperature) and the dorsal columns (vibratory sensation, position sense and discriminative sensation). Sensory deficit from a spinal nerve lesion is distributed in a dermatome pattern. Sensory deficit from a peripheral nerve lesion is in the distribution of that peripheral nerve. Sensory deficit from a polyneuropathy will have a stocking and glove distribution because the longest axons are the most affected.

Cerebellar Signs

Dysarthria in cerebellar disease consists of slowness, slurring of words and scanning speech. In scanning speech, the patient's voice varies from a low volume to a high volume as if scanning from peak-to-peak. Cerebellar disease produces a spluttering *staccato speech*. For example the word *artillery* will be spoken as *ar-til-lery*. Cerebellar lesions result in nystagmus, dysmetria of saccades, jerky pursuit eye movements. Cerebellar nystagmus occurs predominantly during volitional use of the eyes and thus is gaze evoked.

Cerebellar lesions impair the gait and stance (the standing posture). To compensate for unsteadiness of stance and gait, the patient assumes a broad-based stance and a broad-based gait. Subtle abnormalities may be better picked by asking patient to do tandem walking.

Dysmetria (past pointing) should be looked for. The patient, in seeking a specific end point, such as the nose on the finger-to-nose test, frequently *undershoots* or *overshoots* the target because of failure to control the muscular contractions that set the distance. *Intention tremor* is a type of tremor that occurs predominantly on voluntary activity and the tremor reaches its peak of oscillation toward the end of the movement. It disappears at rest. It is noticed dramatically when reaching for objects (such as when performing finger-to-nose testing).

Dysdiadokokinesia means difficulty in performing rapid alternating movements. It means only incoordination of muscular contractions during rapid alternating movements. Cerebellar lesions produce inaccuracies in rapidly repeated movements.

Incoordination of limbs is tested by the finger nose test for the upper limb and heel-shin test for the lower limbs. The heel-to-shin test for in coordination supplements gait testing in bedridden patients. Patients with cerebellar disease are often hypotonic. Hypotonia is much more apparent with acute than with chronic lesions. Pendular reflexes result because of the presence of cerebellar hypotonia. In a normal patient, the leg normally stops swinging after one or two excursions during the knee jerk. In a patient with cerebellar disease, the leg swings to and fro several times, like a pendulum, without the normal checking of the excursions by muscle tone.

Table 2 Primitive reflexes with age of appearance and disappearance

Reflex	Appears	Disappears
Grasp	Birth	3–4 months
Moro	Birth	3–4 months
Rooting	Birth	3–4 months
Stepping	Birth	3–4 months
Placing	Birth	3–4 months
Sucking	Birth	3–4 months
Asymmetric tonic neck reflex	Birth	3–6 months
Landau reflex	3 months	1–2 years

Meningeal Signs

Meningeal signs are present when the meninges are inflamed from infection or the presence of blood. *Meningismus* is the presence of meningeal signs. *Meningism* is the presence of neck stiffness in the absence of meningeal inflammation. The various maneuvers used to elicit meningeal signs produce tension on inflamed and hypersensitive spinal nerve roots and the resulting signs are postures, protective muscle contractions or other movements that minimize the stretch and distortion of the meninges and roots. These include neck rigidity, Kernig's sign and Brudzinski's sign.

Assessment of Primitive Reflexes and Postural Responses

These need to be performed in young children, and children with developmental delay and suspected cerebral palsy. Primitive reflexes are normally present in the newborn but these normally disappear by 3 months to 1 year of life. These primitive reflexes have to be lost so that voluntary functions can be acquired. Abnormal persistence is a clue to a likelihood of developing cerebral palsy. The primitive reflexes, with the age of appearance and disappearance are summarized in **Table 2**. The abnormalities to be noted are (i) continued presence of a reflex that should have disappeared, (ii) asymmetric response or (iii) absence of an expected reflex.

Postural responses are mechanisms which children develop to support themselves against gravity and to develop equilibrium and balance. The appearance of these at the appropriate times is essential for normal development. Some of the important postural mechanisms include the tilt reactions. Tilt reactions develop when the child is 9–12 months of age. With the patient in sitting position, the patient is tilted to one side, then forward and back. During the sideways tilt, the child's arm abducts and extends to the side as a protective mechanism. This test also helps in early detection of subtle hemiplegia as the reaction will be absent on the affected side. During the forward tilt, the child extends the head and back. During the backward tilt, the child flexes the head and back.

Motor Screening Examination

This can be performed in children older than 4 years of age. If any abnormalities are found, then detailed testing needs to be performed. Whenever possible, the examiner should try and demonstrate what needs to be performed. The child needs to be encouraged and praised to improve cooperation.

- The child should be asked to hop, first on one foot, and then the other.
- He should be asked to tandem-walk, toe-walk and heel walk.
- The child should be asked to rise from the squatting position. A Gower's sign suggestive of proximal muscle weakness may be seen.

- The child should be asked to stand with the feet close together, eyes closed and arms stretched out. The Romberg's sign and any abnormal movements may be looked for.
- The child should be asked to perform the finger-nose-finger test.

Schema of Neurological Examination of Child Younger than 2 Years of Age

In a young child, the child should be observed carefully while on the mother's lap during the history taking process. Some assessment of cranial nerve abnormalities, squint, facial dysmorphism, quality and symmetry of limb movements and any abnormal movements and postures may be observed. The examination must initially be continued while the child is still in the mother's lap. The head, muscle tone, deep tendon reflexes, plantar responses, sensation, response to sound and visual tracking can be tested. Methods of tone assessment have been described in **Box 2**. The pupillary responses should be noted. Hand the child a toy. Early handedness (before the age of 2 years) is a sign of congenital hemiplegia. Look for the maturity of the grasp and see if it is age-appropriate.

After this, the mother is asked to place the child on the examination table. Here the spontaneity of limb movements, the quality of movements, the presence of antigravity movements, the presence of any asymmetry, the developmental reflexes, response to pull to sit, traction response are assessed. Systemic examination should also be completed at this stage. Head circumference should be measured. Sensory examination in infants is difficult and usually limited to gross touch and pain.

In the end, the child is placed on the floor and assessment of crawling, walking and running is done. The child may be encouraged to do this by rolling a ball or a toy across the floor so that he tries to retrieve it. Asymmetries, waddling, foot drop, or scissoring may be noted.

MORE ON THIS TOPIC

Iype M, Sharma S, Sankhyayan N. Evaluation of Neurological System. In: Gupta P. Clinical Methods in Pediatrics. 3rd ed. New Delhi: CBS; 2014.

Paine RS, Oppe TE. Neurological examination of children: clinics in developmental medicine, vol 20/21. London: William Heinemann: 1966.

Spillane J. Bickerstaff's Neurological Examination. In: Clinical Practice. 6th ed. USA: Blackwell Science Publishers; 1996.

Swaiman KF. General aspects of the patient's neurological history. In: Swaiman KF, Ashwal S, Ferriero DM. Pediatric Neurology: Principles and Practice. 4th ed. Philadelphia: Mosby Elsevier; 2006. pp. 1-16.

Swaiman KF. Neurological examination after the newborn period until 2 years of age. In: Swaiman KF, Ashwal S, Ferriero DM. Pediatric Neurology: Principles and Practice. 4th ed. Philadelphia: Mosby Elsevier; 2006. pp. 37-64.

Swaiman KF. Neurological examination of the older child. In: Swaiman KF, Ashwal S, Ferriero DM. Pediatric Neurology: Principles and Practice. 4th ed. Philadelphia: Mosby Elsevier; 2006. pp. 17-35.

IN A NUTSHELL

1. A comprehensive neurological evaluation which includes a detailed history, physical examination, and the judicious use of investigations is the key to reach the diagnosis in children with neurological problems.
2. A thorough history is the best pointer towards the diagnosis, and guides the examination and investigation techniques to be used.
3. The developmental history of the child (premorbid) and current status (normal or regression) is an essential component of evaluating a child with neurological problems.
4. The chief aspects of the child's disease that need to be obtained by history include the age at onset, the type of onset, the parts of the neuroaxis involved and the type of progression.
5. Neurological examination needs to be tailored to the child's age, general condition and likely etiological possibilities.
6. The traditional neurological examination can be done in older children and adolescents, however, the scheme and detail of examination needs to be modified for infants and young children.

Chapter 42.2
Cerebrospinal Fluid and Neurophysiology
Anita Choudhary

CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) is principally formed by secretion from ependymal cells of choroid plexus of the lateral, third and fourth ventricles. The rate of CSF formation in healthy adult is approximately 20 mL/hour. Total CSF volume in full term neonate is approximately 50 mL, whereas in adult it is approximately 150 mL.

Cerebrospinal fluid provides buoyancy and protects brain tissue from injury (from head movement and trauma), it redistributes in response to acute change in any intracranial content (helps to maintain normal intracranial pressure), serves as a route for the transport of centrally produced hormones, supplies nutrients to nervous system tissues and removes waste metabolites.

Flow of Cerebrospinal Fluid

Cerebrospinal fluid flows from the lateral ventricles into the third ventricle through the interventricular foramina (foramina of Monro) and then into the fourth ventricle through the cerebral aqueduct. From fourth ventricle CSF enters central canal of spinal cord or exits the ventricular system through the lateral foramina of Luschka and the midline foramen of Magendie to enter subarachnoid space via cisterns. Flow of CSF is mainly downward posterior to the spinal cord and upward anterior to the cord, finally reaching the basal cisterns, from where it flows mainly over the brain convexity.

Cerebrospinal Fluid Examination

Cerebrospinal fluid examination is the most important investigation for diagnosis of meningitis and encephalitis. It is often helpful in evaluating CNS demyelinating disorders, Guillain-Barré syndrome, intracranial hypertension (as in idiopathic intracranial hypertension), neurodegenerative disorders, collagen vascular diseases, leptomeningeal carcinomatosis, subarachnoid hemorrhage (in patients with negative CT scan) and neurotransmitter diseases. The diagnostic value of lumbar puncture (LP) was first recognized and described by Quincke in 1891.

Contraindication for lumbar puncture (1) Local sepsis at the site of the LP; (2) Suspected raised intracranial pressure; (3) Thrombocytopenia or other bleeding diathesis (platelet count < 20,000/mm^3, INR > 1.4), (anticoagulation therapy should be avoided for at least 2 hours following LP) and (4) In a critically ill patient, LP is withheld temporarily as the procedure may lead to cardiorespiratory compromise. Neuroimaging prior to LP should be considered in immunocompromised state, suspicion of mass lesion, stroke, focal infection, papilledema, altered level of consciousness and focal neurological deficit.

Cerebrospinal Fluid Gross Examination

Opening pressure Opening pressure is measured using a manometer. Normal CSF pressure varies with age. It ranges from 10 mm H$_2$O to 100 mm H$_2$O in young children, 60–200 mm H$_2$O after 8 years of age. In obese adult it ranges from 60 mm H$_2$O to 250 mm H$_2$O. Minor fluctuation in physiological ICP occurs with heartbeat (2–5 mm H$_2$O), breathing (4–10 mm H$_2$O) and Valsalva maneuver. Opening pressure above 250 mm of H$_2$O is diagnostic of intracranial hypertension. Raised intracranial pressure is noted in various pathological states, including meningoencephalitis, brain abscess, brain tumor, intracranial bleed, idiopathic intracranial hypertension.

Appearance (Clear, turbid, xanthochromic) Normal CSF is crystal clear like water. Elevated white blood cell (WBC) count (> 200/mm^3) or red blood cell (RBC) count (> 400/mm^3) will cause CSF to appear turbid. Xanthochromia (yellowish CSF) is caused by lysis of RBCs (due to hemoglobin breakdown products), hyperbillirubinemia or elevated CSF protein (> 150 mg/dL). CSF may appear orange in hypercarotenemia and treatment with rifampicin. Brown discoloration of CSF may occur in meningeal melanomatosis.

Cerebrospinal Fluid Cytology

In children and adult normal CSF may contain up to 5 WBC/mm^3 (70% lymphocytes, 30% monocytes), while neonate may have up to 19 WBC/mm^3. CSF WBC count is increased in meningitis, encephalitis, central nervous system (CNS) demyelinating disorders, immunological disorders and malignancy. CSF lymphocytosis is seen in viral, fungal and tubercular infection of CNS, although in earlier stage of illness a predominance of polymorphonuclear leukocytes (PMNs) may be seen. CNS demyelinating disorders, GBS, brain and spinal cord tumor, collagen vascular diseases and chemical meningitis may also cause CSF lymphocytosis. In bacterial meningitis predominant CSF cells are PMNs, however, approximately 10% of bacterial meningitis cases will show a lymphocytic predominance (defined as > 50% lymphocytes or monocytes), especially early in the clinical course and when there are fewer than 1,000 WBCs/mm^3.

Traumatic tap results in an artificial increase in WBC count by approximately one WBC for every 700 RBCs in the CSF. In patients with an abnormal hemogram, the direct calculation is corrected by the observed plasma ratio: Predicted WBC (CSF) = RBC (CSF) × [WBC (plasma)/RBC (plasma)]. If traumatic tap occurs, CSF is collected in three consecutive tubes and cell count is measured. If the number of RBCs is relatively constant, then it is assumed that the blood is caused by an intracranial hemorrhage. A falling count suggests traumatic tap. This three-tube method, however, is not always reliable. Neoplastic cells, eosinophils and plasma cells within the CSF are always considered abnormal.

Cerebrospinal Fluid Biochemistry

Glucose CSF glucose is approximately two-thirds of plasma glucose measured during the preceding 2–4 hours. CSF glucose levels generally do not go above 300 mg/dL. CSF glucose concentration below 40 mg/dL (hypoglycorrhachia) or a ratio of less than two-thirds of the plasma glucose level is considered abnormal. Bacterial meningitis can cause decreased CSF glucose levels. A low CSF glucose level is uncommon in viral meningitis but has been reported in mumps, herpes simplex, and herpes zoster meningoencephalitis. Noninfectious conditions like meningeal carcinomatosis, sarcoidosis, chemical meningitis, hypoglycemia, and subarachnoid hemorrhage may cause lowered CSF glucose concentration.

Protein In normal infant and adults, CSF protein concentration in the ventricular compartment is (6–15 mg/dL), in the cistern magna 15–25 mg/dL, and 20–50 mg/dL in the lumbar sac. The CSF protein concentration is high (up to 150 mg/dL) in the neonate, the adult value is reached between 6 months and 12 months of age. Elevated CSF protein is seen in CNS infections, intracranial hemorrhage, Guillain-Barré syndrome, CNS demyelinating disorders, brain and spinal cord tumor, myxedema and status epilepticus. Protein concentration is spuriously elevated by the presence of RBCs in a traumatic tap situation. 1 mg/dL of protein is increased for every 1,000 RBCs/mm^3. This correction is only accurate if the same tube is used for the protein and cell counts. Very high CSF protein content may be observed in a spinal cord tumor, arachnoiditis,

and other reasons leading to complete spinal CSF obstruction. Low CSF protein levels can occur in conditions such as repeated LP or a chronic leak, in which CSF is lost at a higher than normal rate. Elevation of CSF immunoglobulin G (IgG), which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis (SSPE), postinfectious encephalomyelitis, and in some cases of multiple sclerosis. CSF oligoclonal bands are present in multiple sclerosis.

Other metabolites Cerebrospinal fluid lactate concentrations are elevated in patients with bacterial infections and in mitochondrial encephalopathies. CSF hypoglycorrhachia and low lactate value in the absence of systemic hypoglycemia is virtually diagnostic of glucose transporter type 1 (GLUT 1) deficiency syndrome. Early onset nonketotic hyperglycinemia shows elevated CSF glycine levels; certain type of intracranial tumors may lead to elevated alpha (α)-fetoprotein, human chorionic gonadotropin, polyamines and astroglial protein concentrations. CSF biogenic amines should be measured in suspected pediatric neurotransmitter disorders.

Cerebrospinal Fluid Examination for Microorganism

Gram stain permits a rapid and accurate identification of causative bacteria in 60–80 of untreated cases of bacterial meningitis. Yield of Gram stain depends on causative organism, and concentration of bacteria in CSF [colony forming units (CFU)]. Greater number of CFU ($> 10^5$ CFU/mL) increases the likelihood of getting positive results. Centrifuged samples should be used for staining. Acid fast staining should be done if tubercular meningitis is suspected. India ink preparation may show organism in approximately 50% cases of cryptococcal meningitis.

Cerebrospinal fluid culture on 5% sheep blood agar and enriched chocolate agar is gold standard for diagnosis of bacterial meningitis. The first 1–2 mL of CSF, even traumatic should be stained and cultured for organisms. Antibiotic treatment prior to LP decreases the sensitivity of culture.

Latex agglutination (LA) allows rapid detection of bacterial antigens in CSF. LA shows good sensitivity in detecting antigens of common meningeal pathogens, i.e., *Haemophilus influenzae* type B (78–100%), *Streptococcus pneumoniae* (67–100%), *Streptococcus agalactiae* (69–100%) and *Neisseria Meningitides* (50–93%). Some experts suggest using LA in cases of suspected bacterial meningitis if the initial Gram stain and bacterial culture are negative after 48 hours. Polymerase chain reaction (PCR) is rapid and sensitive test for diagnosis of viral meningoencephalitis. PCR has sensitivity of 95–100% for diagnosis of herpes simplex virus type 1 (HSV1), enterovirus, Epstein-Barr virus meningitis.

Complications of Lumbar Puncture

Lumbar puncture is a relatively safe procedure, but minor and rarely major complications may occur even when aseptic measures and good technique are used. Pain and paresthesias in the distribution of a lumbar nerve root resulting from contact with the needle during procedure may occur. (*Caution*—reposition the needle toward the midline). Permanent nerve injury is highly unlikely. Postprocedural headache: occurs in approximately 10–33% patients, may occur within 72 hours of procedure, it gets relieved with supine position. Rare complications include intrathecal infection, cerebral herniation, bleeding and formation of epidermoid tumors (which can be avoided by using spinal needle with proper fitting stylet).

In rare situations CSF may be obtained from ventricles, ventriculoperitoneal shunt and cistern. A reservoir (Ommaya) can be implanted in patients requiring repeated withdrawal of CSF or repeated intraventricular medications; this allows safer and more convenient access.

Subdural tap may be done as diagnostic/therapeutic tool for subdural collection (effusion or blood).

Ventricular Tap

A ventricular tap is indicated for the removal of CSF directly from lateral ventricle of a patient with hydrocephalus and open anterior fontanel, which shows life-threatening raised intracranial pressure not responding to conservative management. A patient with closed anterior fontanel requires surgical approach to reach ventricular system. The procedure carries significant risk of infection, hemorrhage and parenchymal brain damage.

NEUROPHYSIOLOGY

Neurons and muscle cells membrane have a stable resting membrane potential. During depolarization ion channels open up and movement of sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) occurs, generating action potentials. These signals are transmitted between neurons through synapses. The action potentials are recorded as waveforms in the laboratory.

Neurophysiologic tests have an important role in the diagnostic evaluation and management of the infant or child with neurological dysfunction. Commonly performed neurophysiological studies in pediatric patients include electroencephalography (EEG), and evoked responses [brainstem auditory evoked potentials, visual evoked response (BAEP, VER)], nerve conduction study (NCS) and electromyography (EMG). Other neurophysiological tests include polysomnography, somatosensory evoked potentials (SSEP) and electroretinography.

Electroencephalography

Electroencephalogram is the recording of the electrical activity from the cortical neurons recorded by amplifying voltage differences between specifically placed electrodes. EEG is recorded by applying electrodes on the scalp, cerebral cortex or inside the brain. Potential difference between the electrodes are amplified and recorded. Electrodes are named according to the underlying area of the brain, e.g., frontal (F), frontopolar (Fp), temporal (T), occipital (O), parietal (P) and central (C) **(Fig. 1)**. All electrodes on right side are assigned even numbers and left side odd numbers. A particular combination of placement of electrodes is called a *montage*. The EEG recording is made up of a number of channels. In a single
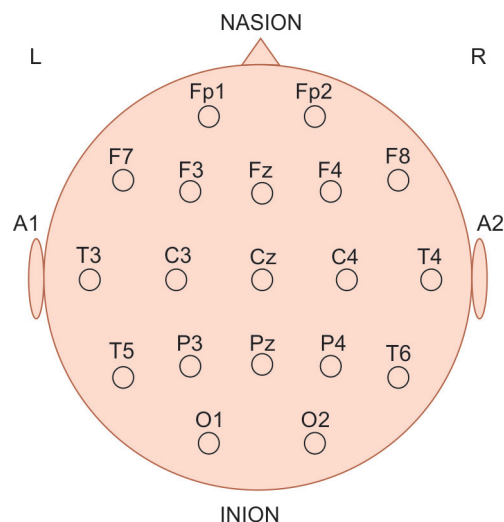
Figure 1 Numbering and placement of electrodes
Abbreviations: Fp, frontopolar; F, frontal; T, temporal; O, occipital; P, parietal; C, central; z indicates midline electrode.

recording multiple montages are used. The two common montages used are the bipolar montage and the referential montage.

Electroencephalographic waveforms These are classified according to their frequencies, shape and site. These usual EEG waveforms are broken down into the following ranges:

- Delta (δ) below 3.5/s
- Theta (θ) 4–7.5/s
- Alpha (α) 8–13/s
- Beta (β) 14–30/s

These waveforms are influenced by many factors, including age, state of alertness (awake or sleep), eye closure, drugs and pathological states. Normal EEG has a wide range of variation in different age groups. Proper knowledge of normal evolution and maturation of various sleep and awake rhythm is important for EEG interpretation. The posterior rhythm attains α range of 8 Hz by 3 years of age **(Fig. 2)**. Abnormalities of waveform include spikes, sharp waves and slow waves. Certain EEG features are diagnostic for particular epilepsy syndromes, e.g., 3 Hz spike wave discharge in childhood absence epilepsy **(Fig. 3)**. Various activation procedures (hyperventilation, intermittent photic stimulation, sleep and sleep deprivation, etc.) are used to increase yield from EEG. During EEG, various artifacts (signals of noncerebral origin) are also recorded. Artifacts can be physiological or nonphysiological origin. It is also very important to identify and try to minimize artifacts.

Indications of Electroencephalography **(Box 1)**

- As an aid to clinical diagnosis of epilepsy
- Classification of seizure and epilepsy syndrome
- Diagnosis of nonconvulsive status epilepticus
- Diagnosis of certain diseases like SSPE
- Presurgical evaluation of epilepsy
- Determination of brain death.

BOX 1 **Important considerations for electroencephalography**

- Electroencephalography remains the principal investigation for children with epilepsy.
- Normal interictal EEG does not always rule out epilepsy, though repeated EEG and activation procedures may increase yield to 80%.
- An abnormal EEG does not always mean epilepsy, epileptiform EEG pattern occur in approximately 1–2% of patients with no history of epileptic seizures.
- Normal EEG variants may be confused for epileptiform discharges.
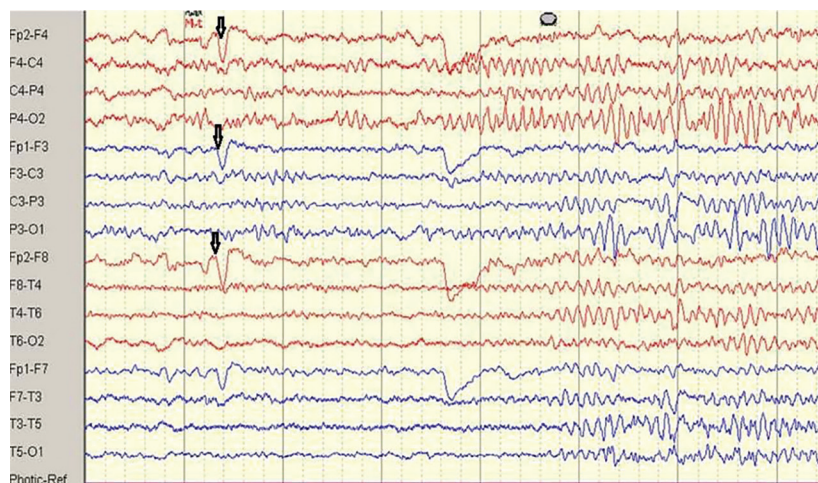
Figure 2 Posterior background alpha (α) rhythm in a 9-year-old boy with eye blink artifacts (arrows) in longitudinal bipolar montage
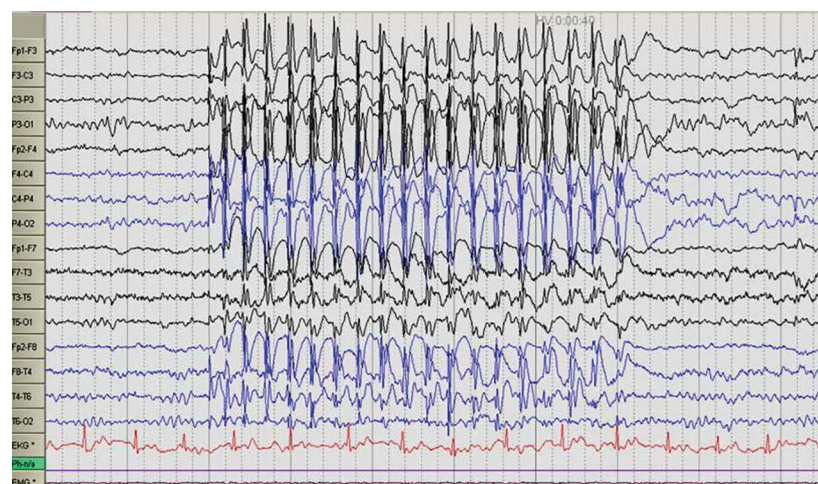
Figure 3 Electroencephalography (EEG) record of a 10-year-old boy with absence seizure showing classical generalized 3 Hz spike and wave discharges in longitudinal bipolar montage

Ambulatory EEG Continuous EEG is recorded during normal activities. It is useful in evaluation of seizure frequency and determination of nature of clinical event.

Video electroencephalography (VEEG) Video-EEG refers to continuous EEG recording with simultaneous video recording of the clinical manifestations. It is useful for differentiation of epileptic seizure from nonepileptic event and characterization of epileptic seizure. It has important role in presurgical localization of epileptogenic focus. It is expensive and long-term VEEG requires hospital admission.

Magnetoencephalography (MEG) Magnetoencephalography refers to mapping of brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain. Magnetic fields are less distorted than electric fields by the skull and scalp, which results in a better spatial resolution of the MEG. Indications of MEG for pediatric patients are detecting spontaneous epileptiform activities and mapping eloquent cortices of motor, sensory and language. Magnetic source imaging refers to the superimposition of magnetoencephalographic signals with magnetic resonance imaging (MRI) to improve spatial resolution compared with surface EEG.

Evoked Potentials

Evoked potential or evoked response refers to electrographic response of nervous system to variety of sensory stimuli. In clinical practice, commonly performed evoked responses are visual evoked potentials (VEPs; flash and checkerboard types), BAEPs and short latency SSEPs. Sensory stimulus leads to generation of sequence of waves, the latencies and amplitudes of waves represent conduction and processing of sensory information in peripheral and central pathway.

Brainstem Auditory Evoked Potentials

Brainstem auditory evoked potentials assess integrity and functional status of both the peripheral (acoustic nerve) and central auditory pathways in the brainstem. BAEPs comprise of five or more positive waves occurring within 10 ms of auditory stimulus **(Fig. 4)**. Different waves are generated at different sites along the auditory pathway **(Table 1)**. Peak and interpeak latencies are compared with normative data. BAEP matures to adult pattern over a period, from birth to 18–24 months of age. Various waves mature at different ages. In clinical practice BAEP is used for:

• Hearing assessment in infants, children and uncooperative patients
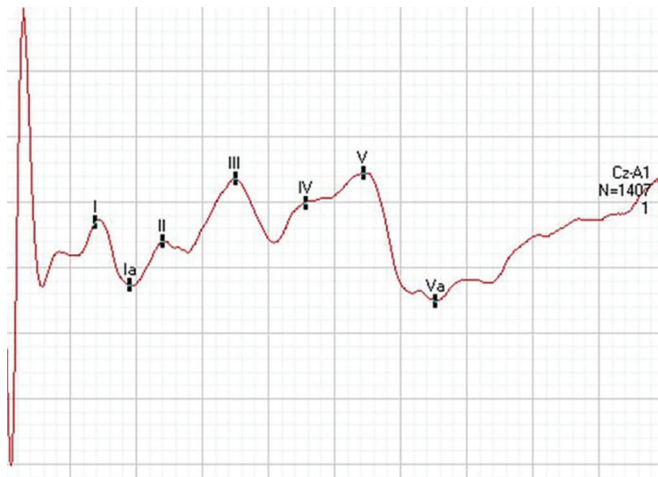
Figure 4 Normal brainstem auditory evoked potential (BAEP) of a 6-year-old boy at 60 dB. Sweep time 1 ms/div, sensitivity 0.2 mV/div

Table 1 Origin of various waves in brainstem auditory evoked potential (BAEP)

Wave I	Cochlear nerve
Wave II	Dorsal and ventral cochlear nucleus
Wave III	Superior olivary nucleus
Wave IV	Lateral lemniscus
Wave V	Inferior colliculus

• Patients with meningitis (for hearing loss)
• For the diagnosis of demyelinating diseases (MRI is more informative)
• Extramedullary and intramedullary brainstem tumors (MRI is more informative)
• Prognosis of comatose patients (metabolic or structural lesions)
• Suspected brain death.

Interpretation

• *Wave I:* Small amplitude, delayed or absent may suggest cochlear lesion
• *Wave V:* Small amplitude, delayed or absent may suggest upper brainstem lesion
• *Wave I–III inter-peak latency:* Prolongation may indicate lower brainstem lesion.
• *Wave III–V inter-peak latency:* Prolongation may indicate upper brainstem lesion.
• *Wave I–V inter-peak latency:* Prolongation may indicate whole brainstem lesion. Shortening of the interval with normal latency of wave V indicate cochlear involvement.

For hearing evaluation in children, the earphones should be comfortably placed on the child's ears. For neonatal screening, 70 dB hearing level clicks are presented at 11 Hz. Hearing is then more closely assessed using 30 dB clicks presented at the rate of 61 Hz. Any infant without a response at 30 dB should be followed up at 3 months.

Somatosensory Evoked Potential

Short latency somatosensory evoked potential refers to electric potential generated by large diameter sensory fibers in the peripheral and CNS in response to electrical stimulus. Commonly performed SEPs are median, peroneal and posterior tibial SEP. SSEP is helpful in evaluation of myelitis, myoclonus and prognosis of comatose patient.

Visual Evoked Potential

Visual evoked potentials **(Fig. 5)** test the function of visual pathway from retina to the occipital cortex. VEP can be elicited by flash of lights or by checker board. Peak latency and amplitudes of the waves are measured. On flash VEP latency, amplitude and morphology of adult VEP are achieved by 6 months of age. VEP is helpful in diagnosis of prechiasmatic, chiasmatic and postchiasmatic lesions. Patterned stimuli VEP can be recorded from birth and may be used as a measure for assessment of visual acuity in preverbal child. Abnormal VEP can be recorded in demyelinating disorders, tumors, neurodegenerative disorders and developmental disability.

Electroretinography

Electroretinography (ERG) is a test to measure the electrical response of retina (rods and cones) in response to light stimuli (flash of lights or patterned stimuli). By 1 year of age ERG amplitudes are comparable to adult value. ERG is helpful in diagnosis of various
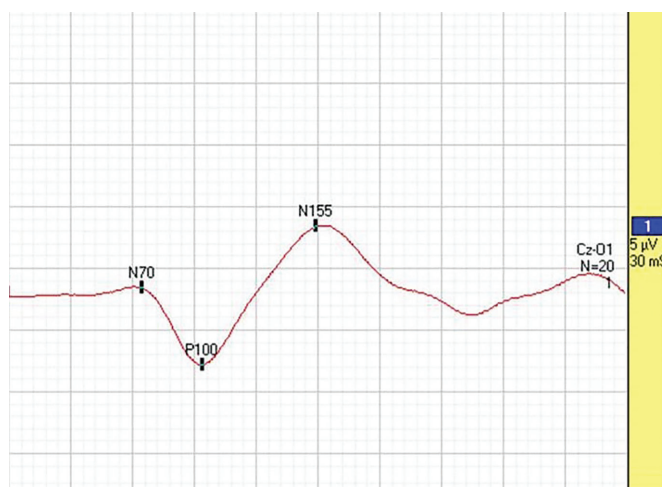
Figure 5 Visual evoked potential (VEP) showing N70, p100, N155 waveforms. Sweep time 30 ms/div, sensitivity 5 mV/div

diseases of visual system (retinitis pigmentosa, photoreceptor dystrophy, Leber's hereditary amaurosis and retinal trauma).

Polysomnography

Polysomnography is useful in evaluation of various sleep disorders, i.e., sleep apnea, narcolepsy, periodic limb movement disorder and parasomnias. The nocturnal polysomnography measures various biophysiological parameters during sleep, i.e., EEG (2–4 channel), eye movements (electro-oculogram), chin and leg electromyogram, respiratory efforts (thoracic and abdominal), heart rhythm (ECG) and oxygen saturation. After completion of test scoring is done for sleep and sleep related events.

Nerve Conduction Studies

Nerve conduction study is a diagnostic modality, used to evaluate function (conduction of electrical impulses) of motor and sensory nerves in response to electrical stimulation of nerve. Standard NCS typically include motor nerve conduction, sensory nerve conduction, F waves and H reflexes. Amplitude, latency and conduction velocity of generated action potentials are analyzed. Motor and sensory nerve conduction velocities in the neonatal period are about half of adult value; with steep conduction increase during the 1st year of life, adult values are reached around 4 years of age. In demyelinating disorders of nerve, distal latency is increased and velocity decreases, whereas in axonal injury amplitude decreases. Repetitive nerve stimulation test is done for disorder of neuromuscular transmission.

Electromyography

Electromyography is a diagnostic procedure to assess electrical activity produced by skeletal muscles. Two kinds of EMG are done:

surface EMG or intramuscular (needle) EMG. In needle EMG, an EMG needle is inserted in muscle belly and insertional activity, spontaneous activity (fasciculation, fibrillations, end plate noise and myotonic discharges) and motor unit action potential are analyzed. It aids in diagnosis of diseases of nerve, neuromuscular junction and muscle. EMG leads to transient rise in serum creatine phosphokinase (CPK) levels.

IN A NUTSHELL

1. Properly interpreted CSF examination is a key tool in the diagnosis of a variety of diseases.
2. Electroencephalography is the most useful laboratory investigation in patients with epileptic seizure.
3. Knowledge of normal maturation pattern of EEG waveforms and normal variants is essential for proper interpretation of EEG.
4. Evoked potentials assess the integrity or functional status of both the peripheral and the central (brainstem, subcortical and cortical) pathways in response to various stimuli.
5. Brainstem auditory evoked potential along with otoacoustic emission (OAE) is an effective screening tool in evaluation of hearing in newborn with high sensitivity (100%) and specificity (96–98%).
6. Polysomnography is important diagnostic tool in sleep medicine.

MORE ON THIS TOPIC

Cascino GD. Use of routine and video electroencephalography. Neurol Clin. 2001;19:271-87.

Chuang NA, Otsubo H, Pang EW, Chuang SH. Pediatric magnetoencephalography and magnetic source imaging. Neuroimaging Clin N Am. 2006;16: 193-210, ix-x.

García A, Calleja J, Antolín FM, Berciano J. Peripheral motor and sensory nerve conduction studies in normal infants and children. Clin Neurophysiol. 2000;111:513-20.

Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med. 2001;345:1727-33.

Jasper HH. The 10-20 electrode system of the International Federation. Electroencephalogr. Clin Neurophysiol. 1958;10:371-5.

Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics. 2010;125:257-64.

Mishra UK, Kalita J. Brainstem auditory evoked potential. In: Mishra UK, Kalita J. Clinical Neurophysiology. 2nd ed. New Delhi: Elsevier; 2006. pp. 329-46.

Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. Pediatrics. 2006;117:741-53.

Pitt MC. Nerve conduction studies and needle EMG in very small children. Eur J Paediatr Neurol. 2012;16:285-91.

Seehusen DA, Reeves MM, Fomin DA. Cerebrospinal fluid analysis. Am Fam Physician. 2003;68:1103-8.

Chapter 42.3
Neuroimaging
Atin Kumar, Jyoti Kumar

Advances in modern imaging techniques have greatly improved our understanding of the pathology of central nervous system in children. Various imaging techniques now available can provide us with both structural and functional information.

Ultrasonography (US) is usually the first imaging modality used in newborns and infants, as it is widely available, can be done at bedside and does not involve ionizing radiation. Magnetic resonance imaging (MRI) and computed tomography (CT) have greatly evolved over the years to give us high-quality images. The advent of multidetector CT scan has greatly reduced the imaging time of the scan, markedly reducing the incidence of motion artifacts. Near isotropic data obtained on multidetector CT gives us excellent multiplanar reconstructions. However, CT involves use of ionizing radiation. MRI, on the other hand, gives superb soft tissue resolution without the use of ionizing radiation. Advances in MR hardware and software have also improved the speed of MR scanning. However, motion artifacts may still be a problem on MR images, especially if the patient is not well sedated. Imaging parameters for acquisition of optimal images in the pediatric population varies from those used in adults, especially newborns and infants, because of the varying chemical composition of developing brain.

Functional imaging techniques like magnetic resonance spectroscopy (MRS), functional MRI (fMRI), nuclear imaging techniques like positron emission tomography (PET) and single photon emission CT (SPECT) can allow us to study neural function across the brain and provide a map of neural activity. Functional neuroimaging techniques can depict the activity of brain during cognitive tasks, thus enabling neuroscientists to study differences in pediatric and adult population that can further help to design treatments tailored to patients in the pediatric age group.

In this chapter we will discuss about the basics of the various neuroimaging techniques and practical aspects for interpreting them. Detailed discussion about imaging appearances of various pathologies will be discussed within each respective chapter in the book.

CRANIAL SONOGRAPHY

The presence of an open anterior fontanel during the 1st year of life provides a window for ultrasound evaluation of the brain **(Figs 1A to F)**. Progressive improvements in software technology, and probe designs have improved image quality and resolution of both anatomy and pathology on ultrasound. The addition of Doppler imaging has further provided an impetus to the role of ultrasound in evaluation of the pathological processes involving the brain. Ultrasound does not use ionizing radiation and causes minimal disturbance to a sick neonate. The most extensive use of cranial sonography is for diagnosis and monitoring of brain injury in the premature infant at high-risk for intracranial hemorrhage and hypoxic ischemic injury.

However, there are several limitations to evaluation of the brain by ultrasound. Transfontanel imaging is usually done in the coronal and sagittal planes which is different from the axial images we routinely see on CT or MRI. It is an operator-dependent technique with limited views of the posterior fossa and convexities. Fresh intraventricular hemorrhage may not be immediately identified on US unless it clots. It is less sensitive for subarachnoid and surface hemorrhage than CT.

Ultrasonography is sensitive to ventricular dilatation and minor degrees of ventricular asymmetry. Ventricular dilatation can result from a variety of causes, intraventricular hemorrhage being a common cause in neonates. This may either arrest, regress to normal or progress to hydrocephalus. Ventricular dilatation may also be a result of *ex-vacuo* dilatation secondary to volume loss due to global insult. Ultrasound is a useful modality to monitor changes in ventricular size, to assess the placement of shunt tip and can also be used for ventricular or lumbar taps as a temporizing measure before shunt placement.

The ventricle to hemispheric ratio is calculated from measurements on both sides in the axial plane. Normal values are between 0.2 and 0.33. Slightly higher ratios have been found in preterm infants (0.32–0.36); term values being achieved at about 36 weeks of gestation.

Doppler ultrasound consisting of pulse wave, continuous wave, and color flow Doppler imaging can be used to assess blood flow in many pathological states including hypoxic ischemic damage, congenital malformations and to assess the need for shunt placement in hydrocephalus **(Figs 2A to C)**.

COMPUTED TOMOGRAPHY

Since radiation dose is always an issue in pediatric patients, choice of CT as an imaging modality must be made with caution. In comparison with CT, MRI has much superior soft tissue resolution with greater sensitivity for acute ischemic damage, assessing myelination patterns and white matter disorders. The advantages of CT include its wide availability and reproducibility. Also, the scan is not as operator independent as ultrasound. Major applications of CT include evaluation of acute cerebral trauma, pathology involving skull bones and orbits, temporal bone and paranasal sinus pathology, follow-up of CSF shunt, evaluation of subarachnoid hemorrhage and craniosynostosis **(Fig. 3)**.

On a CT scan the structures which attenuate the radiation the least appear dark (hypodense) and which attenuate the radiation the most appear bright (hyperdense). The intermediate structures show the varying shades of gray. Hence, air appears absolutely hypodense followed by fat which is slightly more attenuating (more gray than air), followed by liquid (CSF in brain). The soft tissues show higher attenuation than fluids. The bone, calcifications and metallic densities appear the brightest and are maximum hyperdense. The bleeds also appear hyperdense in acute stage. Contrast enhancement is also seen as hyperdense lesions. The attenuation is quantitatively measured in terms of Housesfield units (HU). Thus the HU value is least for air (around –900), more for fat (–90 to –10), about 0–20 for fluids, 20–60 for soft tissues, 100–200 for contrast enhancements and 200–800 for calcifications, bone and metallic structures.

Axial images on CT are obtained parallel to the canthomeatal line using a slice thickness of 2.5–5 mm. To reduce the radiation dose, coronal images may be obtained by reconstructing the axial images. With the advent of multidetector CT, we can obtain nearly isotropic data for high quality multiplanar reconstruction. In cases of craniosynostosis, scans of 3 mm or lesser thickness should be obtained and three dimensional reformations of the bones can then be obtained by using specialized software to assess suture patency.

Contrast medium is administered when looking for infectious, neoplastic or vascular pathology **(Fig. 4)**. Contrast is administered in a dose of 2 mL/kg of body weight. CT angiogram (CTA) may be
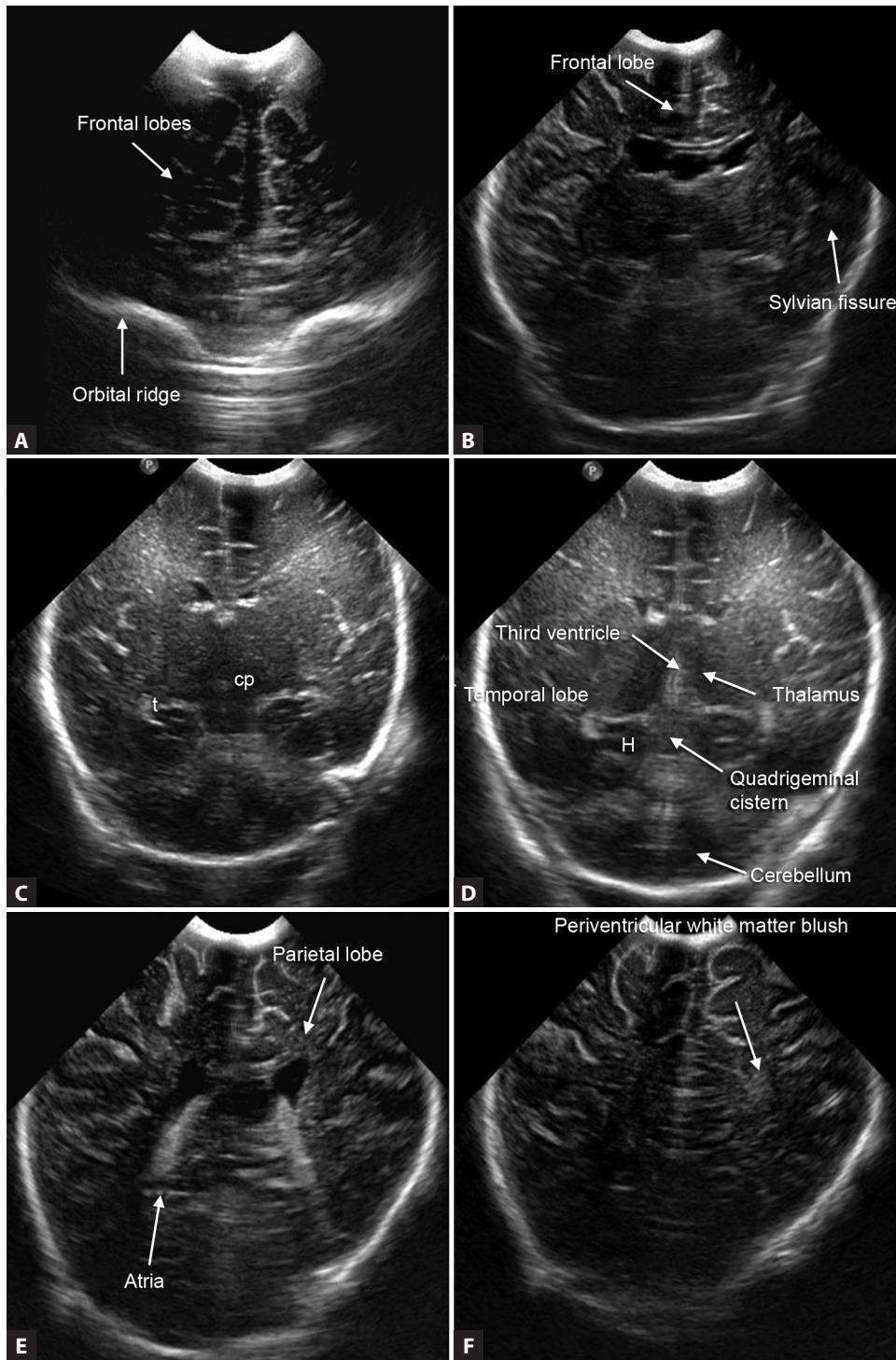
Figures 1A to F Coronal images from anterior to posterior at the level of (A) Anterior frontal lobes; (B) Sylvian fissures; (C) Temporal horn (t)/cerebral peduncles (cp); (D) Hippocampi; (E) Occipital horns/atria and (F) Occipital lobes

done for vascular anomalies like arteriovenous malformations or aneurysms.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging provides multiplanar imaging with excellent spatial and contrast resolution without repositioning the patient or the machine. Its advantages over CT scan include no harmful effects of ionizing radiation, better resolution and no bone interference with soft-tissue resolution. Its advantages over ultrasound include better resolution and no limitation of timing as it can be done even after fontanel closure contrast from ultrasound which requires acoustic window for cranial examination and hence possible before fontanel closure only.
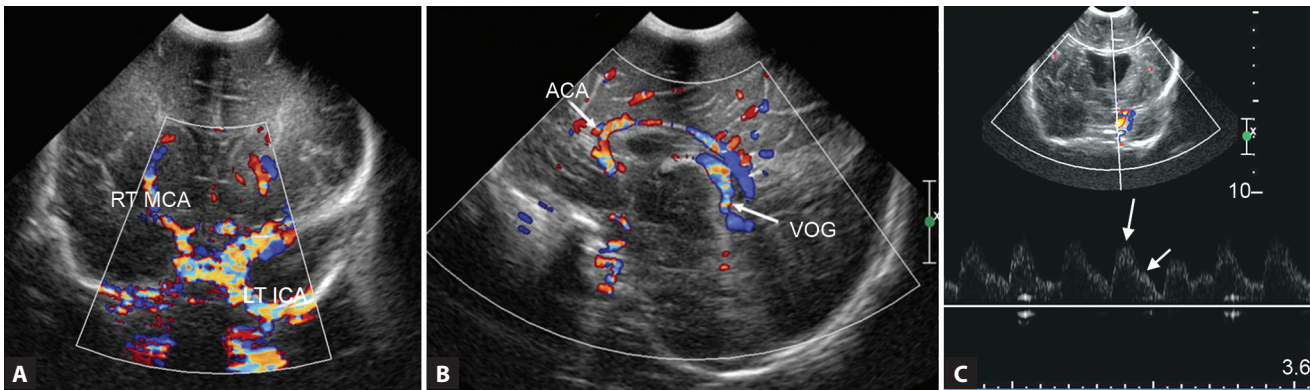
Figures 2A to C (A) Normal color Doppler images through the circle of Willis depicts the internal carotid arteries and their bifurcation; (B) Sagittal sonogram image of the venous system shows patent deep venous system including vein of Galen (VOG). Note made of pericallosal branch of anterior cerebral artery (ACA) and (C) Spectral Doppler of the left internal carotid artery (ICA) depicts continuous forward flow above baseline including rapid systolic upstroke (long arrow) followed by gradual decline in flow in diastole (short arrow)
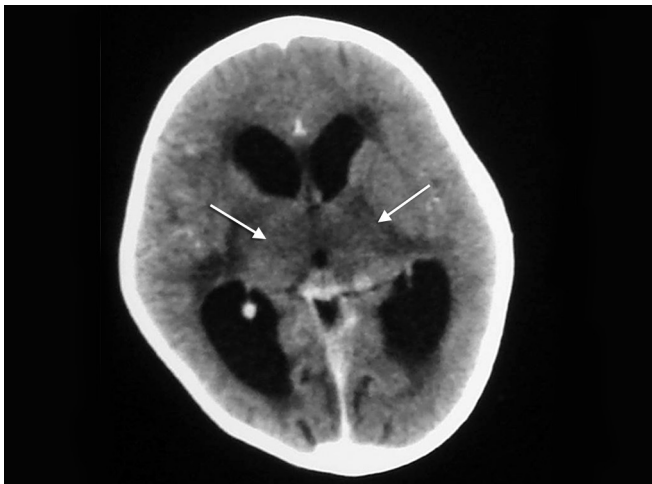
Figure 3 Axial contrast enhanced CT image of the brain at the level of basal ganglia shows hypodensities in bilateral thalami (arrows) consistent with infarcts. *Note:* The dilated lateral ventricles with periventricular hypodensities (ooze)
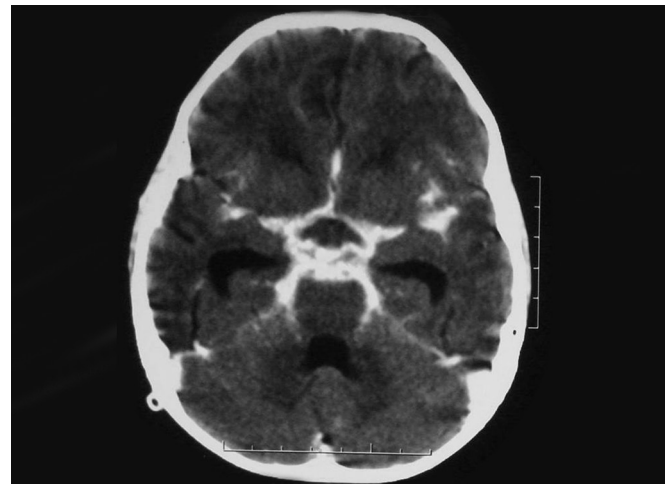
Figure 4 Axial contrast enhanced CT image of the brain at the level of basal cisterns shows densely enhancing exudates in all basal cisterns in tubercular meningitis

The patient is positioned within an MRI scanner wherein a strong magnetic field is created around the area to be imaged. The process requires a strong and uniform magnetic field. Field strength of magnet is measured in Tesla. It ranges from 0.2 to 7 Tesla with 1.5 T and 3 T being the most commonly clinically used magnets. Orientation of the image is controlled by varying the main magnetic field using gradient coils. Radiofrequency pulses are used to obtain high resolution images from the body.

The hydrogen nuclei (protons) present in various tissues of the body are used to generate signals from the body which are detected and processed by the equipment to generate useful images. The noise produced during MR examination is caused by switching on and off of the coils used to generate signal. The signal obtained from different tissues varies depending upon various factors—the density of protons within that particular tissue, the mobility of protons within the molecular lattice (referred to as T1 relaxation), the effect of local magnetic fields produced by magnetic nuclei within the tissue (referred to as T2 relaxation) and susceptibility effects from paramagnetic ions (e.g., from Fe ions in bleeds) on local magnetic fields within tissue (referred to as T2* relaxation).

The MRI uses different programmed imaging sequences like spin echo (SE), fast spin echo (FSE), gradient-recalled echo (GRE) and inversion recovery (IR) to obtain images from the tissues. These sequences use the above-mentioned factors in varying weightage to generate different signals from different tissues. Hence, all of these, i.e., SE, FSE, GRE and IR sequences can be used to produce a T1-weighted (T1W) image or a T2-weighted (T2W) image.

The production of a T1W or a T2W image is controlled by two main parameters—time to echo (TE) and time for relaxation (TR). Keeping a short TE (in the range of 12–25 s) and short TR (in the range of 450–600 s) produces T1W image whereas a long TE (in the range of 100–120 ms) and a long TR (in the range of 3,500–4,500 ms) produces a T2W image. A short TE and a long TR produces a proton density (PD) image which is solely dependent on density of hydrogen nuclei within the tissue.

T1-weighted image predominantly uses the T1 relaxation properties of tissues to differentiate them from each other. Herein tissues with short T1 relaxation times like fat and intracellular and extracellular methemoglobin (seen in hemorrhage) produce a high

signal intensity (bright or hyperintense) whereas tissues with long T1 relaxation times like fluid (CSF in brain), soft tissues, muscle, deoxyhemoglobin and hemosiderin produce low signal intensity (dark or hypointense). As a general rule most of the tissues and pathologies appear hypointense or isointense on T1W images. It is easier to remember the exceptions, i.e., tissues which show hyperintense signal on T1W image—fat, subacute hemorrhage (containing methemoglobin), high protein content fluid (within some cysts), melanin, slow flowing blood in vessels, calcification (sometimes) and contrast material like gadolinium. On a T1W image of the brain in a child when myelination is complete (above 2 years of age) the gray matter appears gray and white matter appears white (hyperintense) **(Fig. 5A)**.

T1-weighted image is useful for anatomy and for postcontrast examination. It is generally not used for detection of pathologies but is rather used to characterize and localize the pathologies detected on a T2W image. One important use of T1W image is after administration of MR contrast agent. Postcontrast T1W images are good for visualization of blood vessels and also shows enhancement of lesions with blood brain barrier (BBB) breach like infections, tumors, subacute stages of infarct.

T2-weighted image predominantly uses the T2 relaxation properties of tissues to produce contrast resolution between them. The tissues with long T2 relaxation times like fluid (CSF in brain), edema—vasogenic or cytotoxic (seen with most pathologies including infarcts, demyelination, tumors, etc.) and extracellular methemoglobin (in hemorrhage) appear hyperintense whereas tissues with short T2 relaxation like cortical bone, deoxyhemoglobin, hemosiderin and muscle appear hypointense. Hence, as a general rule most of the tissues and pathologies appear hyperintense on T2W images. The only exceptions which appear isointense or hypointense on T2W image include air, calcification, early and late hemorrhage (containing deoxyhemoglobin or hemosiderin), melanin, iron or other mineral deposition, high protein content fluid and fast flowing blood in vessels (called as flow voids). On a T2W image of the brain in a child when myelination is complete (above 2 years of age) the gray matter appears gray and white matter appears dark (hypointense) **(Fig. 5B)**.

Inversion recovery sequences are typically used to selectively eliminate or nullify signal from a particular tissue. The most commonly used IR sequence is fluid attenuated inversion recovery (FLAIR) which as the name suggests nullifies the signal from fluid (CSF in brain) **(Fig. 5C)**. FLAIR has got T2W which means the CSF which should have been hyperintense now gets suppressed and appears hypointense. But the other pathologies within the brain parenchyma which produce edema in interstitium still appear bright or hyperintense. Hence, this sequence is more sensitive than simple T2W image to detect subtle hyperintense signal changes especially in regions adjacent to CSF containing ventricles and sulcal spaces **(Figs 6A to C)**.

Gradient-recalled echo sequences (*T2 star or T2**) produce images in which the signal is susceptible to presence of paramagnetic substances like iron or calcium. These images are hence best used for identification of bleeds (containing iron) and calcifications (containing calcium). In general GRE sequences are faster in terms of acquisition time as compared to SE sequences.

Susceptibility-weighted imaging (SWI) is another type of technique which uses sequences which enhance the magnetic inhomogeneities of iron and calcium and produce marked hypointense signal (blooming) in areas containing these ions. These sequences are more sensitive than the routine T2* sequences (e.g., FLASH) for detection of bleeds and calcifications **(Figs 7A to C)**. Another advantage of SWI is that bleed and calcifications can be differentiated from each other based on evaluation of various components of SWI which is not possible on over T2* FLASH images.

Diffusion-weighted imaging (DWI) is a technique that uses MRI to measure the diffusion of water through tissues. Diffusion refers to the random (Brownian) motion of water molecules within a tissue which is dependent upon structural and physiologic factors within that tissue. If there is unrestricted diffusion then the chances of motion are equal in all directions—referred to as isotropic diffusion. However, if the structural factors allow diffusion primarily in one direction while restricting the movement in other perpendicular directions then it is referred to as anisotropic diffusion. The prime example of this is white matter fibers because its component axon allows water diffusion only along the long axis and hence in the direction of the tract fiber. If there is restriction of diffusion of water molecules within the tissue then MRI detects it as restricted diffusion. This occurs in the setting of intracellular
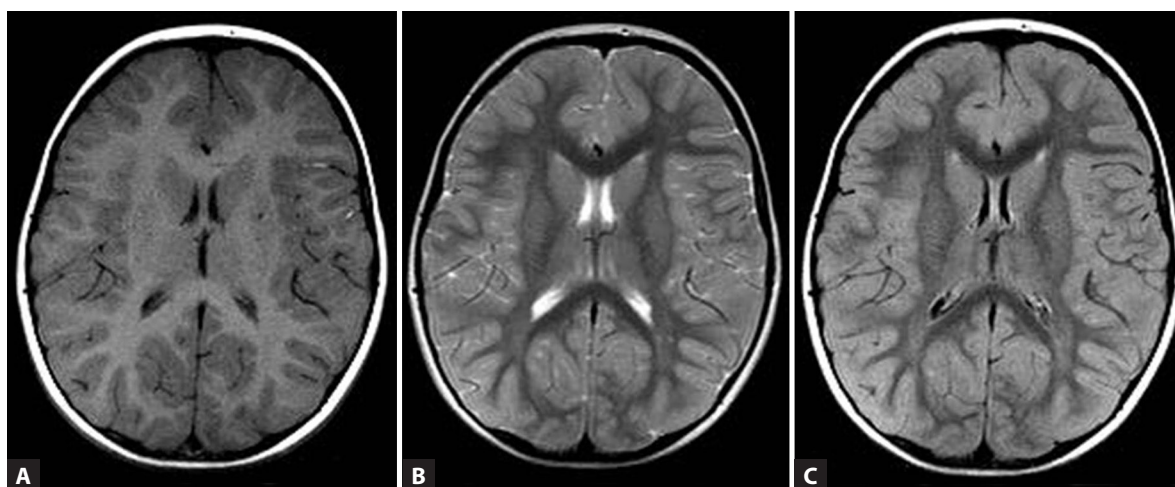
Figures 5A to C (A) T1W; (B) T2W and (C) FLAIR. Axial MR images of the brain at the level of basal ganglia and lateral ventricles. The gray matter is gray on T1W, T2W and FLAIR images but the white matter is white on T1W image and dark on T2W and FLAIR images. The CSF within the ventricles is hypointense on T1W image, hyperintense on T2W image and gets suppressed (becomes hypointense) on the FLAIR image
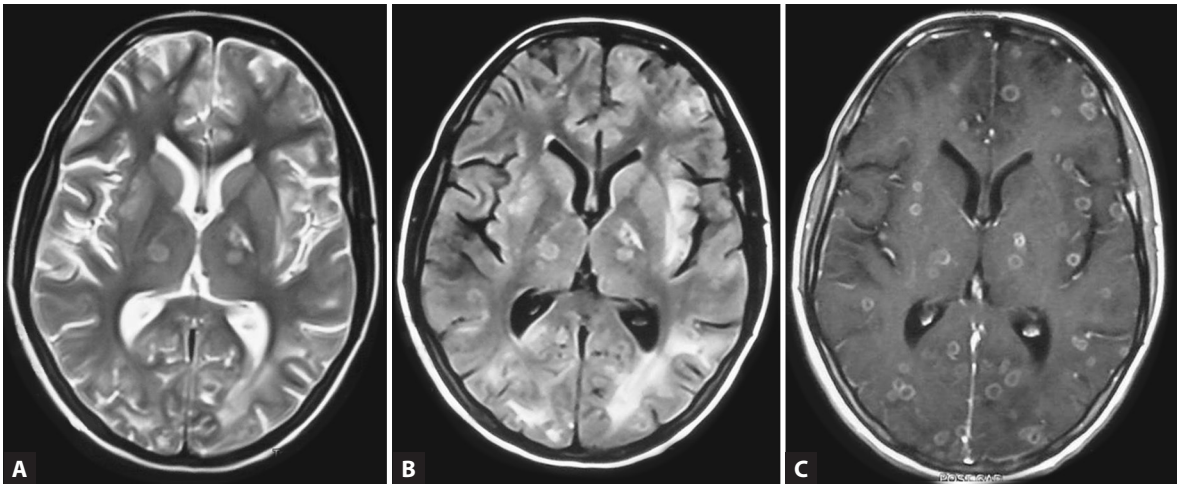
Figures 6A to C (A) T2W; (B) FLAIR and (C) Postcontrast T1W. Axial MR images of the brain in a child of disseminated tuberculomas. The multiple lesions with hyperintense edema are seen on T2W image but are better appreciated on the FLAIR image. The lesions show ring enhancement on the postcontrast T1W image
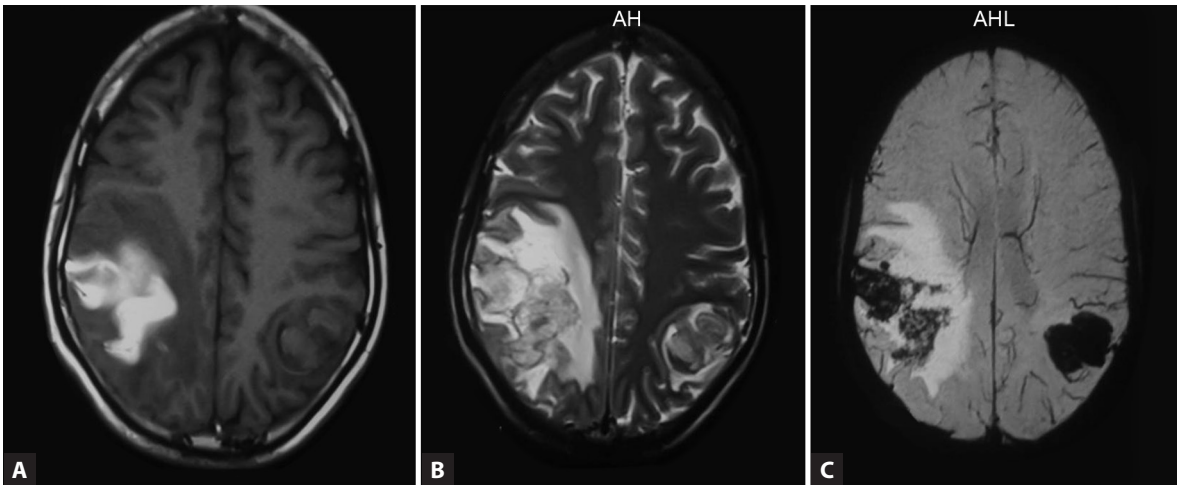
Figures 7A to C (A) T1W; (B) T2W and (C) SWI. Axial MR images of the brain show bilateral parenchymal bleeds appearing hyperintense on T1W and heterogenous on T2W images. *Note:* The *blooming* seen on SWI images. These were secondary to venous sinus thrombosis

cytotoxic edema. The conditions which show restricted diffusion on DWI include infarcts, hypoxic ischemic encephalopathy (HIE), abscesses, certain high-grade neoplasms and some acute demyelinating plaques. Diffusion restriction is best seen in acute phase and gradually diminishes with time. Hence, in acute pathologies, timing of examination from initiation of symptoms is important for correct interpretation of DWI images. For example in acute infarct **(Figs 8A to C)**, the diffusion restriction can be seen as early as within an hour of insult (even before changes are seen on conventional T1W and T2W images), show peak restriction by 48–72 hours and then start to decline to become almost normal by 7–10 days.

Diffusion tensor imaging (DTI) is an advanced diffusion technique which acquires diffusion characteristics of tissues in multiple directions. Data generated out of this result in not just quantification of restriction of diffusion but also direction of restriction. DTI images are used to evaluate white matter tracts. If there is loss of anisotropy in a white matter tract it signifies destruction of its anatomic structure. Tractography is the technique used to depict the entire course of a white matter tract **(Fig. 9)**. It has been used to

map white matter tracts in brain and look for any involvement by disease processes like HIE, infarcts and tumors.

Magnetic resonance spectroscopy is an in vivo technique to demonstrate and quantify certain brain metabolites noninvasively. The technique used most commonly in brain studies is proton MRS. The metabolites detected include N-acetylaspartate (NAA) which resonates at a frequency of 2.0 ppm and is a marker of intact neuronal tissue, creatine (Cr) which resonates at 3.0 ppm and is a marker of brain energy metabolism and choline (Ch) which resonates at 3.2 ppm and is a marker of cell membrane and represents cellular density. These three metabolites are consistently seen in a brain spectrum **(Fig. 10)**. NAA level decreases in most diseases causing neuronal or axonal loss and therefore is nonspecific. However, the extent of decrease can quantify the extent of the disease process. NAA levels are increased in Canavan disease and are diagnostic of this condition. It occurs because of deficiency of NAA in Canavan disease, an enzyme which causes breakdown of NAA. Creatine levels are abnormal in diseases of Cr synthesis. Choline levels are high in conditions of excessive cell turnover including proliferative tumors, leukodystrophies,
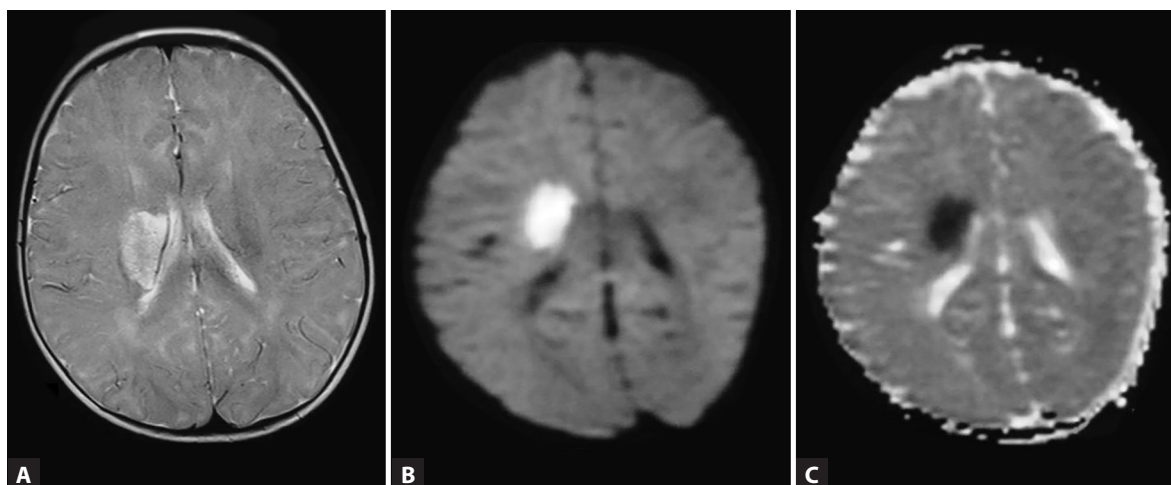
Figures 8A to C (A) T2W; (B) 1,000 DWI image and (C) ADC map. Axial MR images of the brain show an acute infarct in right periventricular region which is hyperintense on T2W image, hyperintense on DWI image and hypointense on corresponding ADC map
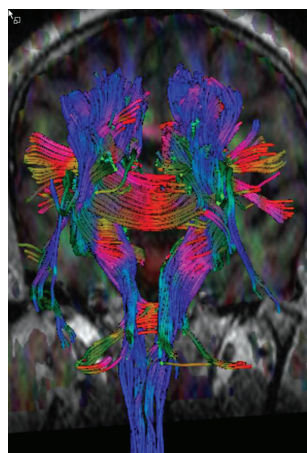
Figure 9 Tractography of brain white matter tracts acquired by DTI shows various white matter tracts coded by colors. Craniocaudal are blue, right to left are red and anteroposterior are green
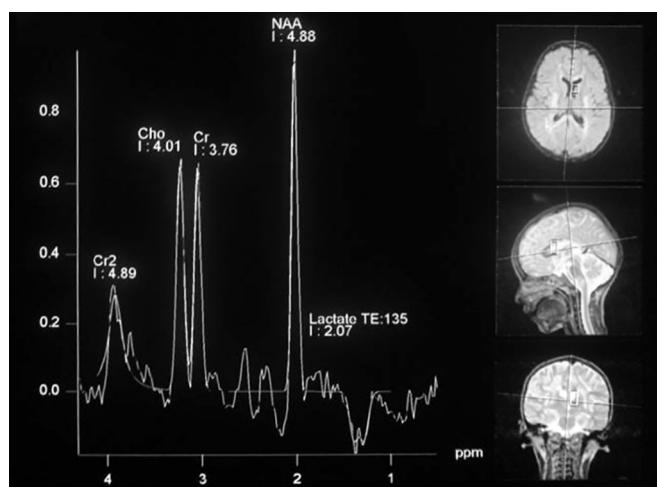
Figure 10 Magnetic resonance spectroscopy (MRS) of the brain showing NAA peak at 2.0 ppm, creatine peak at 3.02 ppm and choline peak at 3.2 ppm. Note also the inverted lactate doublet peak at 1.3 ppm. This was a case of Leigh's disease

demyelination and gliosis. The other metabolites which may be seen include lactate (Lac) which shows a doublet peak at 1.33 ppm and represents anaerobic metabolism. Lac peaks are often seen in tumors with necrosis, mitochondrial disorders and HIE. Lipid (Lip) resonates between 0.9 ppm and 1.3 ppm and is a marker of breakdown of cell membrane and release of fatty acids. Lipid peaks are seen in aggressive tumors and infections. Branched chain amino acids show peak at 0.9 ppm and are elevated in Maple syrup urine disease. Myo-inositol peak is seen at 3.6 ppm and is elevated in glial-based tumors and adrenoleukodystrophy.

Rather than absolute values of individual peaks, it is often the ratios between various metabolites which are used as markers to quantify the severity of disease. The commonly used ratios include Cho/NAA, Ch/Cr and Lac/NAA.

Functional MRI (*fMRI*) is a technique which assesses cortical neuronal activity by indirect method of measuring regional cerebral vascular response. The principle used here is that changes in oxygen saturation of the hemoglobin in blood produces a small change in local MR signal which is known as the blood oxygenation level—dependent (BOLD) effect. The deoxyhemoglobin being paramagnetic in nature produces decreased signal due to local inhomogeneities in magnetic field. However, in response to increased demand (as occurs in stimulation of cortical area), there occurs transient increase in regional cerebral blood flow with increased inflow of oxygenated hemoglobin. This is much more than the cerebral metabolic rate of oxygen and hence there is decreased extraction of oxygen from hemoglobin. This leads to displacement of deoxyhemoglobin by oxygenated hemoglobin which results in increased signal (as deoxyhemoglobin causes decrease in signal). In practical aspects, when a task is given to the patient, the cortical area of brain involved in executing that task shows increased signal on BOLD maps and hence can be mapped. In pediatric population patient compliance remains a practical issue. fMRI has been used in pediatrics for presurgical mapping for epilepsy or tumor surgery and also for studies of cognition and language networks.

Magnetic resonance angiography (MRA) is a group of techniques used to image blood vessels by MRI. It can be arteriography or venography depending upon whether arteries or veins are imaged. The methods used to obtain images can involve flow dependent techniques like *time-of-flight* (TOF) and phase contrast (PC) angiography. TOF is the most commonly used method in brain angiographies **(Fig. 11)**. It gives excellent images without the use of contrast material. But the disadvantages include a long time of
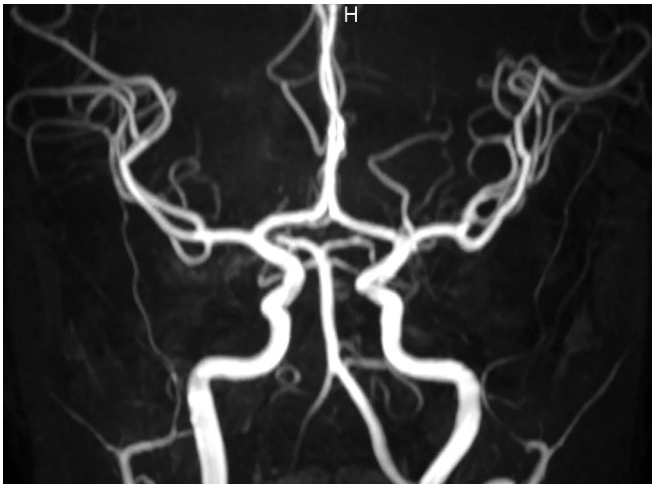
Figure 11 Time-of-flight (TOF) MR angiography of the intracranial arteries (AP projection) shows the major vessels constituting the circle of Willis

Figure 13 Postcontrast T1W axial magnetic resonance (MR) image shows abnormal enhancement (hyperintensity) along the basal cisterns and sylvian fissures consistent with meningitis

acquisition (ranging from 5 min to 15 min) and certain in-plane flow artifacts. MR arteriography is indicated in evaluation of stroke, aneurysms, arteriovenous malformations and Moyamoya disease. MR venography is indicated in suspected cases of venous sinus or cortical venous thrombosis **(Figs 12A and B)**.

Contrast-enhanced MRI can be obtained after administration of intravenous contrast. The most commonly used MR contrast agents are gadolinium based compounds. The indications for usage of contrast remain same as discussed in CT section above and include acute inflammations [infections or acute disseminated encephalomyelitis (ADEM)], tumors, specific white matter disorders like Alexander's disease and adrenoleukodystrophy and for suspected vascular anomalies. Contrast may also be used to perform MRA. Generally T1W images are used to detect contrast enhancements **(Fig. 13)**. The potential contraindications for giving gadolinium contrast agents include patients with acute or chronic severe renal insufficiency (glomerular filtration rate less than 30 mL/min/1.73 m^2) who have a risk of developing complication of nephrogenic systemic fibrosis (NSF). However,

per se the gadolinium agents are not nephrotoxic and may be used in mild decreased renal function wherein CT contrast agents are contraindicated.

The *contraindications for MRI* include electronic devices implanted within body like cardiac pacemaker and cochlear implants and metallic devices which are non-MR compatible like aneurysm clips, metallic stents, metallic coils, orthopedic implants, bullet fragments, etc.

NORMAL MYELINATION

The white matter is unmyelinated to start with. The process of myelination starts at fifth fetal month and continues till 2 years of age. Myelination progresses in a systematic manner from caudal to cephalad, from central to peripheral, from dorsal to ventral and from posterior to anterior. Hence, brainstem and cerebellum myelinate before cerebrum, basal ganglia and thalamus myelinate before deep white matter, posterior limb of internal capsule (PLIC) myelinates before the anterior limb of internal capsule (ALIC),
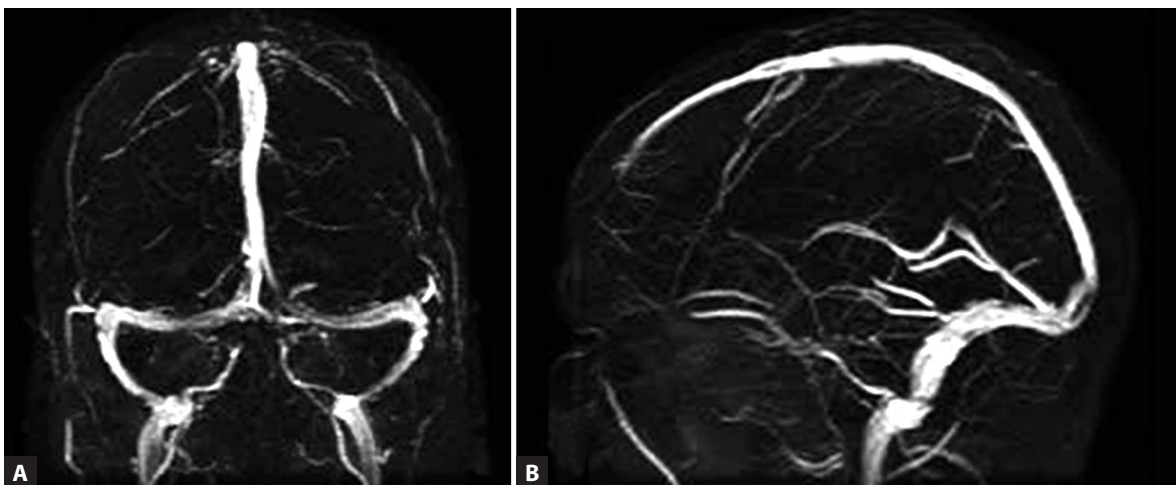
Figures 12A and B (A) Magnetic resonance (MR) venography of the intracranial venous system AP and (B) lateral views shows the major sinuses and cortical veins

splenium of corpus callosum myelinates before the genu and corona radiate myelinates before the subcortical region.

Magnetic resonance imaging is very useful in depicting the myelination process. Unmyelinated white matter due to high water content appears dark on a T1W and bright on a T2W image **(Figs 14A to F)**. When myelination occurs, there is decrease in water content and increase in lipid (or fat) content within the white matter. Hence, it starts to appear bright or hyperintense on T1W image and dark or hypointense on T2W image. It is important to remember here that the changes of myelination are depicted on MRI first on T1W image and after a time gap on T2W image. Hence, a structure which gets myelinated will appear hyperintense on T1W image initially and will become hypointense on T2W image only after a time gap ranging from few weeks to months. Most of the structures show complete myelination by 6 months on a T1W image but take up to 2 years to appear myelinated on a T2W image. So the process of myelination is better appreciated on a T1W image in the first 6 months and on a T2W image after 6 months **(Table 1)**.

Hence broadly the myelination on T2W image lags T1W image by about 2–3 months. The last associative area to mature is peritrigonal region (at the tips of occipital horns of lateral ventricles). This area shows persistent T2/FLAIR hyperintensity in ages up to 3 years. Abnormal hyperintense signal persisting beyond 3 years of age may represent changes of hypoxic ischemic encephalopathy especially if associated with volume loss.

The adult pattern of MR images on T1W and T2W are hence obtained at around 2 years of age **(Figs 15A to F)**. At this time onwards, on a T1W image the gray matter appears gray and the white matter appears white whereas on a T2W image the gray matter appears gray but the white matter appears dark.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography is a molecular imaging technique which generates maps of distribution of positron-emitting-radioisotope-labelled biomolecules in living body. The most common clinically used compound is (F-18) fluorodeoxyglucose (FDG) which maps the glucose metabolism in brain tissue. It thus detects pathological changes earlier than structural imaging techniques like CT and MRI. The images of PET are fused with structural images produced by CT (PET-CT) or MRI (PET-MRI). Hence, the functional changes shown by increased or decreased uptake of FDG are superimposed upon the anatomical images and
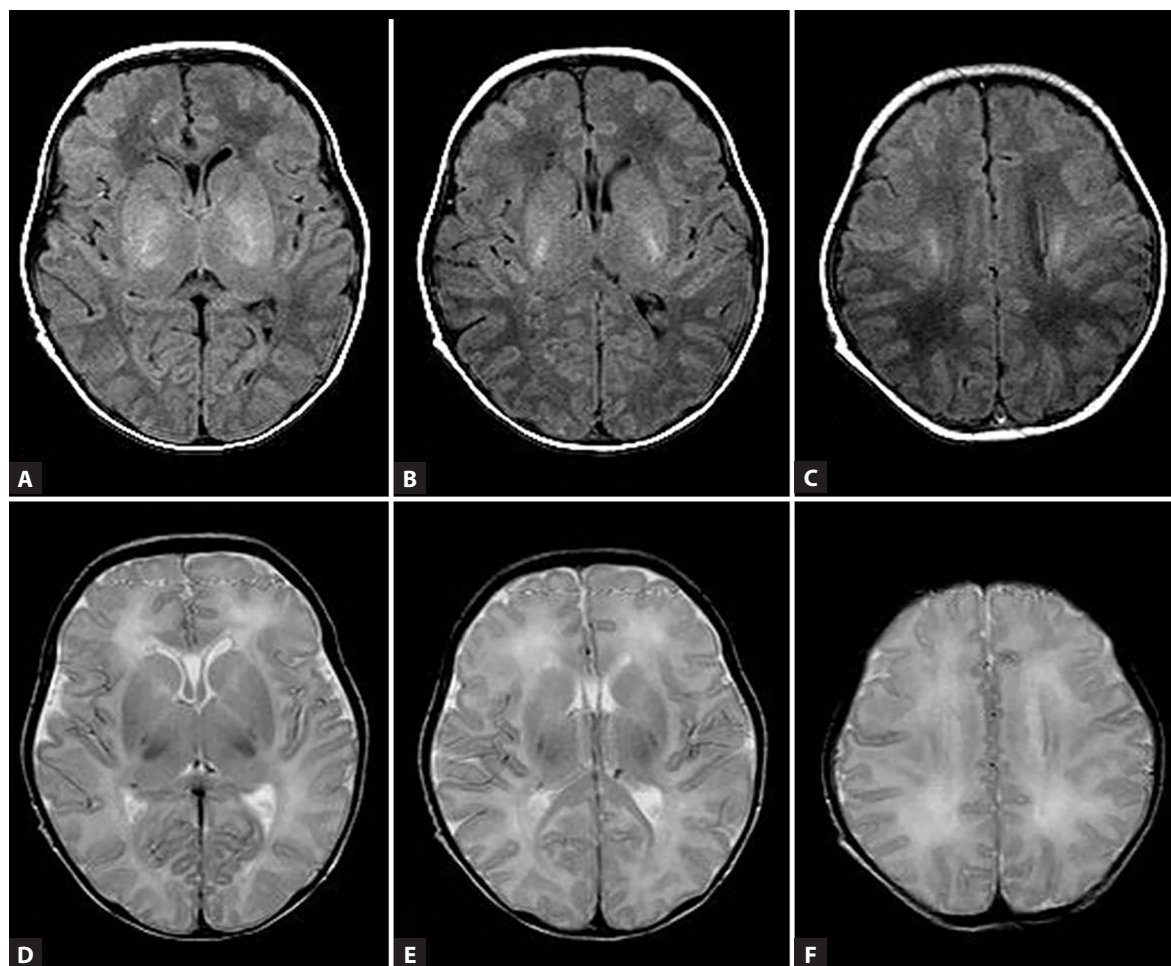
Figures 14A to F (A to C) Axial T1W and (D to F) corresponding T2W magnetic resonance (MR) images of the brain of a normal term neonate. The structures myelinated till now like posterior putamen, ventrolateral thalamus, posterior limb of internal capsule and perirolandic centrum semiovale show hyperintense signal on T1W and hypointense signal on T2W images. The rest of the unmyelinated deep and subcortical white matter shows hypointense signal on T1W and hyperintense signal on T2W images

Table 1 Normal myelination pattern

Age	T1W image	T2W image
Neonate	Dorsal brainstem, brachium pontis, lateral thalamus, PLIC, central corona radiata, perirolandic centrum semiovale and gyri, optic tracts and radiations	Dorsal brainstem, lateral thalamus, PLIC, central corona radiate and rolandic and perirolandic cortex
2 months	ALIC, deep cerebellar white matter	Brachium pontis, optic tracts, perirolandic centrum semiovale
4 months	Central centrum semiovale and splenium of corpus callsoum	Central centrum semiovale
6 months	Complete centrum semiovale, genu of corpus callosum, overall white matter looks bulkier	ALIC, splenium of corpus callosum
8 months	Subcortical white matter of occipital lobe	Genu of corpus callosum
1 year	Subcortical white matter of frontal and temporal lobes	Subcortical white matter of occipital and parietal lobes

Abbreviations: ALIC, anterior limb of internal capsule; PLIC, posterior limb of internal capsule.
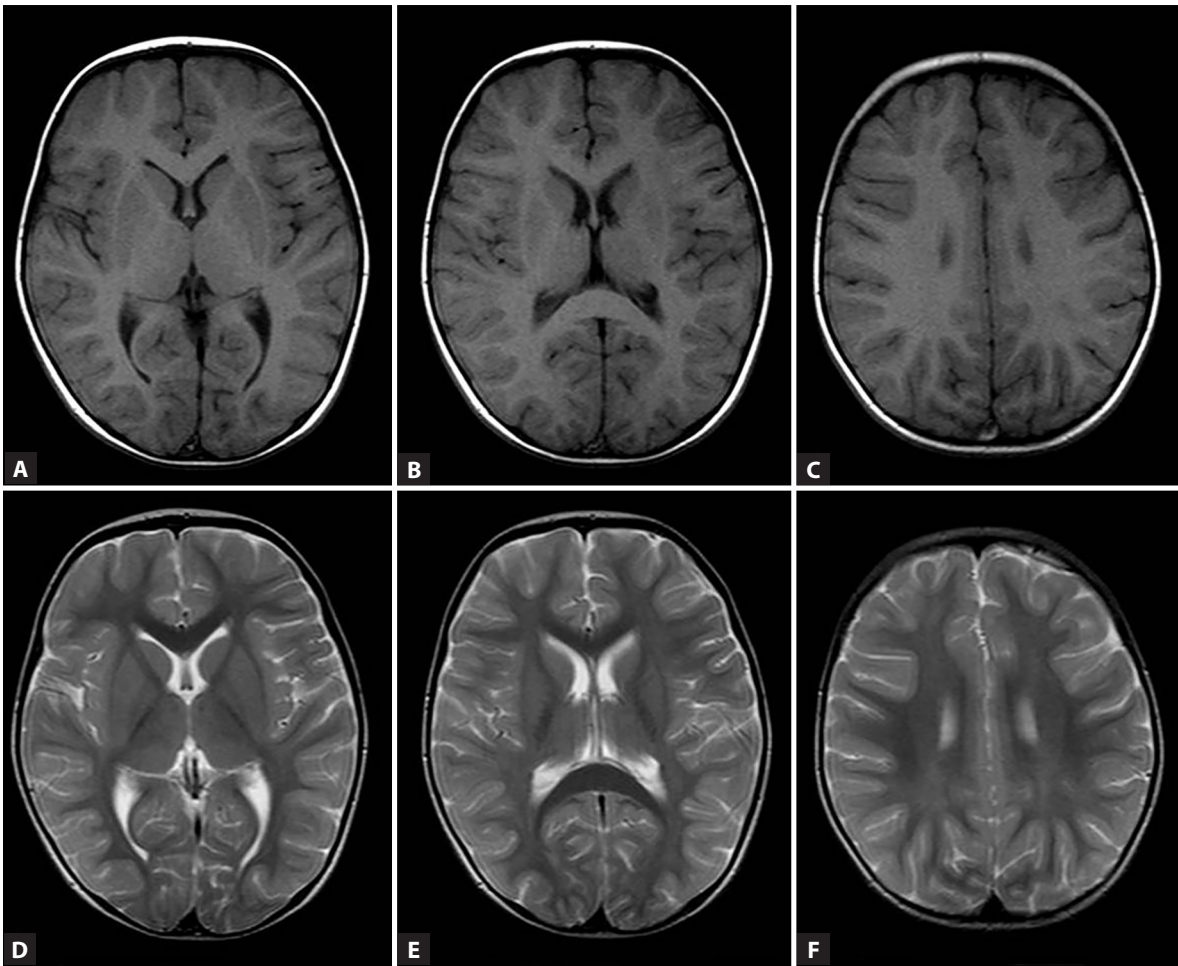
Figures 15A to F (A to C) Axial T1W and (D to F) corresponding T2W MR images of the brain of a normal 2-year-old child. The brain at this time shows adult pattern of myelination with complete white matter including that of both limbs of internal capsule and entire corpus callosum showing hyperintense signal on T1W and hypointense signal on T2W images. Note the gray matter appears gray on both T1W and T2W images

can be mapped to the involved area. With wider availability of PET MR, it is now slowly replacing PET-CT with advantage of decreased radiation exposure.

Fluorodeoxyglucose positron emission tomography (FDG PET) has been widely used in pediatric temporal lobe epilepsy especially mesial temporal sclerosis. It shows hypometabolism during the interictal stage and hypermetabolism during seizures. It also has been shown to have a role in extratemporal seizures wherein cortical foci of hypometabolism may be detected in interictal period. These areas may not be showing any structural changes on CT or MRI. FDG PET also has a proven role in assessing brain tumors. It helps to show the most metabolically

active parts of tumors and hence can help in choosing the part to biopsy or can help in surgical resection. It may also be used to differentiate between residual/recurrent tumor and radiation induced changes.

MORE ON THIS TOPIC

Ball WS. Pediatric Neuroradiology. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1997. pp. 317-26.

Barkovich AJ, Raybaud C. Pediatric Neuroimaging. 5th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012.

Griffiths PD, Paley MN, Whitby EH. Imaging the Central Nervous System of the Fetus and Neonate. 1st ed. USA: Taylor and Francis; 2006.

Saunders DE, Thompson C, Gunny R, et al. Magnetic resonance imaging protocols for paediatric neuroradiology. Pediatr Radiol. 2007;37(8):789-97.

Tortori-Donati P, Rossi A. Pediatric Neuroradiology Brain. 1st ed. New York: Springer; 2005.

Van Wezel-Meijler G, Leijser LM, de Bruïne FT, et al. Magnetic resonance imaging of the brain in newborn infants: practical aspects. Early Hum Dev. 2009;85:85-92.

IN A NUTSHELL

1. The chief neuroimaging modalities in children include ultrasound, CT and MRI.
2. Ultrasound is the initial imaging modality used for evaluation of neonatal and infant brain.
3. Ultrasound is useful to detect intracranial hemorrhage and ventricular dilatation.
4. CT scan is easily available, cheaper and takes less time to perform as compared to MRI but has the risk of ionizing radiation and provides much lesser information.
5. MRI is the procedure of choice for detailed evaluation; It has multiplanar imaging capability combined with excellent contrast resolution and does not have any radiation issues.
6. Disadvantages of MRI include high cost, limited availability and increased time for imaging requiring sedation and/or anesthesia.
7. The advanced MRI techniques including MRS, DWI and fMRI have shown promise in making it a functional study combined with structural imaging.

Chapter 42.4
Neural Tube Defects and Spinal Cord Malformations
Sujata Kanhere

Neural tube defects (NTDs) and associated spinal cord malformations are the most common types of central nervous system congenital anomalies. NTDs are classified as primary defects and secondary defects. Primary NTDs which account for the majority (95%) are caused by failure of spontaneous closure of the neural tube, between the 3rd and 4th week of gestation. Secondary defects (5%) occur later, once the neural tube closes.

Neural tube defects consist of a wide range of malformations along the neuraxis. The common NTDs are spina bifida occulta, meningocele, meningomyelocele (MMC), anencephaly and encephalocele. Other NTDs and malformations of the spine include dermal sinus, craniorachischisis, lipoma involving conus medullaris or filum terminale, tethered cord, syringomelia, diastematomyelia, caudal regression syndrome and iniencephaly.

Neural tube defects affecting the spinal cord are collectively called spina bifida. These defects may be apparent as meningocele or MMC or inapparent (spina bifida occulta). Some of these conditions are benign, some are treatable but often the prognosis is poor and the handicap is severe. Other malformations or anomalies may also be present along with NTDs. The impact of the condition goes beyond the physical disability and psychological effects for the child to affect the entire family in terms of financial and social implications.

Neural tube defects are a result of genetic and environmental factors. Recent advances have led to strategies for prevention of NTDs such as periconceptional folic acid ingestion by women in child bearing age group, which have reduced the occurrence of NTDs by 70% and thus are important for every pediatrician to know. Equally important in prevention is prenatal screening during pregnancy as well as the role of genetic counseling for future pregnancies.

EPIDEMIOLOGY

The incidence of NTDs is 1.5–2.5/1,000 live births worldwide. Every year 3 lakh babies are born with NTDs globally. The incidence varies in different parts of the world and different regions within countries. In United States of America, incidence is 1/1,000 births whereas it is as high as 12/1,000 births in some parts of Ireland and Wales. In 1982, in China the incidence ranged between 2.7/1,000 and 10.6/1,000 births with a high incidence of 7.25/1,000 reported from rural China which has subsequently reduced. Craniorachischisis and iniencephaly are much more frequently seen in Northern China.

A recent systematic review of birth prevalence of NTDs in India found that the overall birth prevalence of NTDs is 4.1/1,000. Anencephaly is more prevalent at 2.1/1,000 births while spina bifida ranked second at 1.9/1,000 births. The incidence of NTDs in North India reported is 3.9–9/1,000 live births while in certain pockets in South India it is as high as 11.4/1,000 live births. The incidence of NTDs in the rural community in India is 6.57–8.21/1,000 live births. The risk of recurrence in the next pregnancy is 4% which increases to 10% and 25% with subsequent pregnancies.

ETIOLOGY

The exact cause of NTDs is not known but the inheritance is multifactorial. A number of environmental factors have been implicated. Hyperthermia, maternal malnutrition, chemicals, maternal obesity, maternal diabetes [insulin-dependent diabetes mellitus (IDDM)], exposure to radiation, alcohol, drugs such as valproate, carbamazepine, trimethoprim, oral contraceptives and clomiphene during pregnancy and specific nutritional deficiencies in mothers during pregnancies such as folic acid deficiency and its role in homocysteine metabolism, vitamin B_{12} deficiency, zinc deficiency, myoinositol and vitamin A seem to play a role in the etiology of NTDs. Periconceptional supplementation of folic acid to women in the child bearing age group had brought down the risk for NTDs by 70%, thus implying a role of maternal folic acid deficiency in the pathogenesis of NTDs. There appears to be a genetic predisposition and mutations in the folate responsive or folate dependent pathways may play a role. NTDs are also seen in Trisomy 13 and 15.

PATHOGENESIS

Failure of normal induction in the process of neurulation at the 3rd week of gestation is responsible for primary NTDs. The neural plate develops from the ectoderm in the 3rd week of gestation. Epidermis is formed from ectoderm by inhibition of bone morphogenetic protein (BMP) and the Wingless (Wnt) signaling pathway. The proliferation of cells within the neural plate causes invagination forming the neural groove in the midline flanked by ridge like neural folds which takes place by day 20 **(Fig. 1)**. Some cells differentiate and migrate to form the neural crest on the lateral surface of the neural tube. The neural folds bend inwards due to changes in the shapes of neural cells to bring the tips of the folds into apposition. Then there is fusion of the tips of the folds leading to formation of the neural tube. This process is called neurulation. The closure of the neural tube initially occurs in the center followed by rapid closure both rostrally and caudally. The rostral end closes by day 23 and the caudal end by day 27 of gestation. Failure of closure of the neural tube leads to formation of most of the NTDs. The vertebral column develops around the central notochord which develops from the notochordal plate.

PATHOPHYSIOLOGY

Genetic Predisposition
Neural tube defects (NTDs) are inherited by a multifactorial trait that follows a threshold model. Those who exceed a threshold liability due to genetic and environmental factors, develop the trait while those below the threshold do not. In NTDs, genetic factors are implicated by the increased recurrence risk for parents of an affected child as compared to general population and familial aggregation of the various types of NTDs. But the recurrence risk still remains low at 3%, much lower than traits caused by a single fully penetrant mutation. Therefore, these defects arise from an interplay of a number of genes along with gene-environmental interactions. Recent studies have implicated polymorphisms in human Vangl 1 and Vangl 2 in infants with NTDs. However, single nucleotide polymorphisms (SNPs) can occur in unaffected persons also.

Pathway relationships associated with NTDs are being increasingly recognized such as the planar cell polarity (PCP) signaling pathway [Wnt and sonic hedgehog (SHH) pathways], DNA methylation pathways, chromatin remodeling and transcription factors. Evaluation of multiple genes may be required in an individual to determine risk as well as appropriate preventive therapy.

Environmental Triggers
Factors found to have an increased risk in nonsyndromic spina bifida are history of previous affected pregnancy (RR 30-fold), inadequate maternal intake of folic acid (RR 2–8 fold increased risk for

(a) At third week of gestation

Ectoderm

Mesoderm

Endoderm

Neural groove

Neural fold

Neural plate

(b) Day 20

Mesoderm

Notochord plate

(c) Neurulation

Neural crest cells

Notochord

(d) Dysjunction

Epidermis (surface ectoderm)

Derivatives of neural crest cells

Neural canal

Neural tube

(e) Secondary neurulation distal to caudal neuropore and formation of filum terminale and conus medullaris

Figure 1 Formation of the neural tube

MMC and anencephaly), pregestational diabetes mellitus (RR 2–10 fold) and antiepileptic drugs—valproic acid and carbamazepine (RR 10–20 fold). Hyperglycemia and hyperinsulinemia increase risk for NTDs. Also maternal periconceptional rise in sugar levels that increase the glycemic index even in nondiabetic women have an increased NTD risk. In addition, a number of factors are suspected to play a role as a risk factor such as maternal vitamin B_{12} status (RR three-fold), maternal obesity (RR 1.5–3.5 fold), maternal hyperthermia (RR two-fold), maternal diarrhea (RR 3–4 fold). Some other risk factors studied but not established are gestational diabetes, chlorination of drinking water, electromagnetic fields, pesticides and hazardous wastes.

Role of Folic Acid

The exact mechanism explaining the association between NTDs and folate is still unknown. The success of folic acid supplementation is because folate metabolism contributes to many biological functions. Folate coenzymes take part in many functions such as DNA and purine synthesis and amino acid interconversion. The methionine produced when homocysteine gets converted to methionine, is used for synthesis of S-adenosyl-methionine (SAM), the body's main methyl donor. SAM participates in methylation of DNA and histones modulating gene expression. Mutations occur in one of the genes encoding enzymes in the homocysteine metabolism as in 5, 10 methylenetetrahydrofolate reductase

(MTHFR). There is an association between a MTHFR variant and mothers of infants with NTD which account for 15% of preventable NTDs.

Maternal Autoantibodies

Neural tube defects can occur in babies of women who had maternal antibodies against folate receptors. The hypothesis is that these autoantibodies block the binding of 3H FA to folate receptors on placental membranes possibly leading to reduced CNS folate which may be responsible for NTDs. In future, this may lead to clinical testing in first pregnancies to adjust the dose of folic acid supplementation in subsequent pregnancies.

Teratogen

Teratogens such as retinoic acid (RA) and antiepileptic drugs are particularly important in the etiology of NTDs. Vitamin A is an essential vitamin for many biological functions. Interestingly in animal embryos, RA can induce NTDs but inactivation of RA synthesis genes or receptor genes in mice lead to high rates of NTDs. Similarly, excessive exposure of human embryos to RA is teratogenic and leads to embryopathy but vitamin A deficiency can also increase the risk of NTD. There is an association of increased risk of MMC with in utero exposure to valproic acid or carbamazepine either as monotherapy or along with other antiepileptic drugs (AEDs). The exact mechanism for increased risk is not known but this happens only when there is a genetic predisposition to the teratogenic effects of valproate.

PREDISPOSED HOST FACTORS: MOLECULAR AND EXPERIMENTAL MODELS

Studies on vertebrates have found a number of factors that are essential for formation of neural tube and its proper closure. It has been suggested that some host factors which are derived from mesoderm are essential to induce neurulation. These factors are chordin, noggin and SHH. The neural tube is patterned along three axes namely anteroposterior, dorsal-ventral and right-left axis as a response to the expression of intrinsic patterning genes and embryonic signaling pathways. The three opposing signal pathways are SHH, Wnt and BMP. SHH induces the differentiation of the floor plate. Fibroblast growth factor, NOTCH, and RA signaling also contribute to neural fate determination. Caudal identity and telencephalic patterning depend on the actions of FGF, Wnt and RA pathways. Homeotic Hox and family transcription factors affect segmental identities and hindbrain features.

CLINICAL PHYSIOLOGY

Failure of closure of the neural tube results in communication with the amniotic cavity and release of substances such as alpha fetoprotein (AFP) and acetylcholinesterase into the amniotic fluid. These substances when found in amniotic fluid serve as biochemical markers of a neural tube defect. Maternal serum AFP

(MSAFP) also rises and can be used as a screening test at 16–18 weeks of gestation to identify pregnancies with risk of NTD.

The clinical presentation depends on the stage of the embryological defect in the process of development of neural tube **(Table 1)**.

CRANIAL DYSRAPHISM

Anencephaly is a NTD due to absence of brain calvaria and is incompatible with life. Encephalocele is formed when there is herniation of brain and meninges through defect in calvaria. Craniorachischisis is defined as anencephaly associated with continuous bony defect of spine with exposure of neural tissue. Iniencephaly is a rare NTD characterized by dysraphism of occipital region classically accompanied by retroflexion of neck and trunk.

SPINAL DYSRAPHISM

Spina Bifida Occulta

This is a common NTD affecting at least 5% of the population. The anomaly consists of a midline defect of the vertebral bodies without involvement of spinal cord or meninges seen usually in the lower lumbar region at L5 S1 levels. The patients are asymptomatic with no neurological signs and the anomaly is detected accidentally on radiographic studies. No treatment is required.

In 10% of certain occult spinal dysraphisms, there may be cutaneous markers over the location of the defect such as tuft of hair, midline lipoma or angioma, pit, lump or dermal sinus over the back **(Fig. 2)**. The roentgenogram of the spine reveals a defect in closure of the posterior vertebral arches and laminae. However, sometimes there may be associated developmental malformations of the spinal cord such as syringomyelia, diastematomyelia or a

Figure 2 Midline lumbosacral cutaneous marker: hypertrichosis

Table 1 Pathological characteristics and their clinical correlates in neural tube defects (NTDs)

Embryological defect	Clinical correlate
Defect of neural folding and formation	Meningomyelocele and anencephaly
Disordered postneurulation development	Encephalocele
Incomplete dysjunction	Dermal sinus, dermoid and epidermoid tumors
Premature dysjunction	Spinal cord lipomas
Disorders of gastrulation	Split cord malformation, neurenteric cysts
Disordered secondary neurulation	Thickened filum terminale, myelocystocele
Failure of development of caudal neuraxis	Sacral agenesis

tethered cord. Ultrasonography (USG) may be helpful for diagnosis in the newborn. Keeping the possibility of these associated malformations in mind, every case of occult spinal dysraphism must be investigated with magnetic resonance imaging (MRI).

Dermal Sinus

A small opening on the skin leads into a narrow passage which may be a dead end or pass through the dura and act as midline cutaneous makers over the location of a meningocele or encephalocele and are found in the lumbosacral or occipital region. Recurrent meningitis of unknown origin should alert one to look for a small dermal sinus. Associated conditions such as diastematomyelia and tethered cord should be looked for and require surgical intervention.

Meningocele

When the meninges protrude out or herniate through the bony defect in the posterior vertebral arches or anterior sacrum, it is termed meningocele **(Fig. 3)**. In most cases, the spinal cord is normal but sometimes there can be tethered cord, syringomyelia or diastematomyelia. Clinically, the meningocele presents as a fluid-filled fluctuant midline lesion. Transillumination is positive as there is no nervous tissue present in the lesion.

Meningomyelocele

This is the most severe and most complex form of spinal dysraphism involving skin, vertebral bodies, meninges, nerve roots and spinal cord **(Fig. 4)**. The dysplastic neural tube is a red, flat disorganized fleshy mass of tissue located in the middle of a cerebrospinal fluid (CSF) containing sac. Usually the sac is present but may rupture leading to CSF leak. Sometimes, the placode is covered by epithelium and a sac may be absent. This is termed myeloschisis.

The location of MMC may be variable but is most often found in the lumbosacral region. The nature and severity of the neurological impairment depends on its location and size. Thoracic defects are more complex and have more complications. MMC in the cervical region are more protuberant. Neural tissue does not lie exposed but is usually covered by thick epithelium. The o tcome is therefore better in these lesions. It can be tethered to adjacent dura. X-ray of the MMC shows the defect of the vertebral arch.

The clinical manifestations of MMC are weakness or paralysis of the lower limbs and bladder and bowel sphincter dysfunction and complications like infection. Hydrocephalus is frequently present **(Fig. 5)**. Often the MMC is associated with developmental

Figure 4 Meningomyelocele

dysplasia of the hip (DDH) and congenital talipes equinovarus (CTEV) or club foot. The spectrum of clinical manifestations varies from severe sensory loss and trophic ulcers to only mild sphincter disturbances. Although intelligence is normal in the majority, cognitive and language difficulties may be present. This may further affect the quality of life of these children.

Urinary Tract and Bowel Dysfunction

Bladder dysfunction occurs because of the interruption of nerve roots in the sacral region as well as fiber connections between brainstem and sacral cord. Additionally, overflow incontinence, loss of sacral tone, loss of sacral and rectal sensations and loss of det usor muscle activity occurs. Normal bladder control is seen in only 0% of patients. Fecal incontinence and constipation are two common problems encountered in a child with MMC.

COMPLICATIONS

Progression or worsening of symptoms in terms of weakness, pain, gait, bladder or bowel function can result from tethering of cord or restriction of growth of spinal cord. Tethered cord may be present even when the child is neurologically asymptomatic. Presence of brainstem symptoms may suggest Chiari II malformation or tethered cord. The two main late complications are hydrocephalus and renal failure.
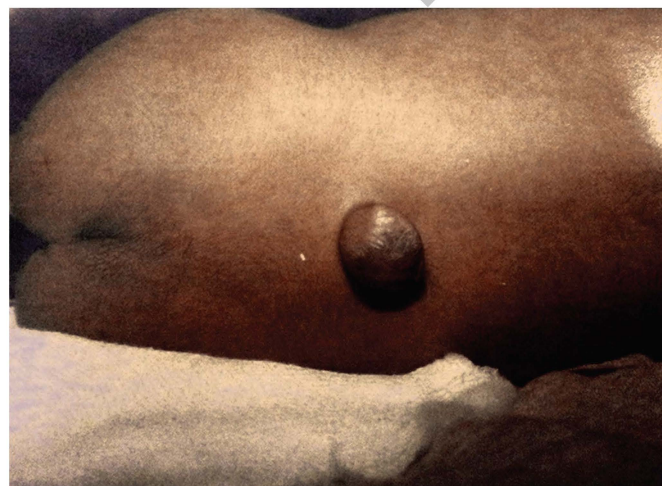
Figure 3 Meningocele

Figure 5 Hydrocephalus and spinal dysraphism in a neonate

Hydrocephalus occurs in 75–80% in children with MMC, while 90% of MMC located in the thoracolumbar region have hydrocephalus. Arnold Chiari II malformation, the most common cause of hydrocephalus in MMC (95%), consists of downward displacement of cerebellar vermis and cerebellar tonsils with the thin long medulla lying parallel to upper segments of atrophic cervical spinal cord. The clinical features are progressive hydrocephalus, secondary brainstem dysfunction, feeding and respiratory complaints including apnea. Hydrocephalus usually develops secondarily after Chiari II malformation because the herniation blocks the hindbrain CSF outflow. In 50–85% of patients, aqueductal stenosis or atresia may also contribute or lead to the hydrocephalus.

Hydronephrosis and renal failure occur following bladder dysfunction and urinary incontinence. Urinary tract infection, particularly bladder infection is seen frequently and vesicoureteral reflux develops by 2–3 years. Renal failure is a late but fatal complication.

Delayed deterioration after repair of MMC may be due to infection, hydrocephalus, malfunctioning or infected shunt, scoliosis, tethered cord, hydromyelia, syringomyelia or a second lesion of occult spinal dysraphism such as dermoid, epidermoid or arachnoid cyst. Additionally, shunt infection is seen in 25%, intellectual deterioration may occur with repeated attacks of meningitis or ventriculitis, epilepsy is present in 10–30%, ocular problems in 30% and all these may contribute to the psychosocial problems in these children.

APPROACH TO DIAGNOSIS

History of any older children born with neural tube defect or associated congenital malformations should be asked for. Maternal illnesses such as diabetes and epilepsy should be noted. Ask for maternal intake of antiepileptic drugs such as valproate, carbamazepine and other teratogens. Symptoms of the child such as movements of the lower limbs, dribbling of urine or bowel incontinence should be noted. Ask for any other obvious congenital anomalies noticed by the parents. In older children, history regarding surgery for lesion or shunt for hydrocephalus should be asked and history about intellectual functioning, gait and psychosocial adjustment should also be taken. Examination is summarized in **Box 1**.

BOX 1 Examination in a child with neural tube defect

- General physical examination for any other congenital anomaly such as club foot, hip subluxation, scoliosis, kyphosis, signs of Chiari II malformation

- Examination of the back to look for the neural tube defect; and presence of associated cutaneous markers

- *Examination of the lesion:* To make a diagnosis of the lesion, presence of leaking, establish the extent and severity

- *Examination of the head:* For head shape and head circumference, anencephaly, encephalocele, hydrocephalus, sutural separation, anterior fontanel, dilated veins on scalp and forehead

- *Neurological examination:* To look for movement of lower limbs, tone, power, reflexes and sensory deficits below the level of the lesion particularly the lower limbs

- *Assessment of bladder function:* Urinary incontinence, urinary retention, spastic bladder, hydronephrosis, urinary tract infection, loss of sphincter tone and loss of sensation over sacral region

- *Examination of anus:* Look for rectal prolapse or patulous anus, sacral or rectal loss of sensation.

INVESTIGATIONS

Antenatal Diagnosis

During pregnancy, MSAFP and fetal ultrasound are the two screening tests that help to identify fetuses at a higher risk for developing MMC or anencephaly. Raised concentration of amniotic AFP in early pregnancy indicates open NTD but there is no such increase in closed NTD. Higher the levels of MSAFP suggest a higher possibility of a NTD. MSAFP screening at 16 weeks of gestation is 64% accurate. AFP levels twice the normal values or more are found in 95% of anencephalic, 80% of open spina bifida and only 2% of normal unaffected pregnancies. Thus implying a high sensitivity, but AFP is not specific for NTD as it can be elevated in open ventral wall defects such as gastroschisis and omphalocele.

Acetylcholinesterase, is another biochemical marker in the amniotic fluid, also produced by fetal CNS, that correlates with MSAFP or amniotic fluid AFP and adds to specificity and sensitivity. A combination of increased ACH and increased AFP is stronger evidence for presence of NTD and has an accuracy of 97%.

Fetal USG helps in differentiating ventral wall defects from NTD and to identify other anomalies, spontaneous leg and foot activity, other spine abnormalities and Chiari II malformation. Confirmation of type and extent of NTD is possible with USG. This serves as a guide for deciding on medical termination of pregnancy (MTP) and therefore preventing births with NTD.

A comparison of accuracy of these screening tests reveals that fetal USG is 60% accurate in low risk pregnancies and 100% accurate when done to confirm a lesion suspected on previous USG. Neither USG alone nor AFP alone is sensitive or specific enough but has a high predictive value when used in combination. Prenatal MRI with ultra fast T2-weighted sequence can visualize the defect and characterize Chiari II and other malformations. 17% of all fetuses with NTD have chromosomal abnormalities such as trisomy 13 and 18, translocation or triploidy. In prenatally detected spina bifida fetal karyotyping and cytogenetic analysis can be done.

Investigations after Birth

X-ray chest and spine, USG of the NTD, head and abdomen, CT scan/MRI brain and spine, karyotyping and cytogenetic analysis should be done. Evaluation and monitoring of genitourinary system by repeated periodic urine culture, renal scans, renal USG, urodynamic studies such as VCUG, cystometrogram (CMG) as required, is a must to reduce need for surgery and to reduce morbidity and mortality.

MANAGEMENT

A multidisciplinary team consisting of the obstetrician, neonatologist, pediatric neurologist, radiologist, pediatric surgeon, neurosurgeon, pediatric nephrologist, neonatal nurse, orthopedic surgeon, physiotherapist and social worker is required for management of a baby born with a NTD.

Parental counseling Antenatal diagnosis or detection at birth of a NTD has to be conveyed to the parents by a knowledgeable and compassionate individual explaining the condition and its extent and severity and also the treatment options available and the prognosis, in a way that parents will understand to help them to accept the condition and take appropriate informed decisions for the child. The parents will require further counseling and support as the child grows.

Fetal repair Prenatal surgery for myelomeningocele by hysterotomy has resulted in correction of hindbrain herniation, reduces the need for shunting and improves motor outcomes at 30 months but may be associated with maternal and fetal risks.

Immediate medical management The neonate should be admitted in the neonatal intensive care unit (NICU) and provided supportive care, with the baby in the prone or lateral position. The lesion must be kept moist by covering with sterile saline dressings. A thorough examination and imaging for ruling out other congenital malformations should be done. Before planning surgery, detailed neuroimaging of spine and head is mandatory.

Surgical Management

Surgery should be performed early to prevent neurological worsening. Surgery consists of repair or closure of the defect. If infection is present, then surgery should be deferred to after treatment with intravenous or intrathecal antibiotics. The timing of surgery depends on whether the lesion is open or closed. If the lesion is open with CSF leak, it should be operated within 24 hours and closed lesions within 48 hours.

Lorber's criteria Surgery is not to be done in the presence of: (1) severe paraplegia at or above L3 level (2) kyphosis or scoliosis (3) gross hydrocephalus (4) associated gross congenital anomalies (5) intracerebral birth injuries or (6) pre-existing ventriculitis. The only treatment option for these children is medical and supportive care.

In addition, other surgical procedures may be needed. (a) Shunt surgery for hydrocephalus (b) Surgical correction of orthopedic conditions (c) Surgical treatment of bladder dysfunction (d) Shunt surgery and sometimes surgical decompression of posterior fossa in Chiari malformation (e) Delayed deterioration after MMC repair may require surgical repair of tethered cord, revised shunting, fenestration of syringomyelia to prevent further deterioration.

PROGNOSIS

Anencephaly is incompatible with life. Untreated MMC has a high mortality rate of 50% with most deaths in the first 4 years of life. If aggressively treated, the mortality rate in MMC is 10–15%. 80–90% of MMC develops hydrocephalus and most require shunt. Intelligence is normal in 70% of cases and almost 60% attend grade appropriate school. Repeated episodes of meningitis or ventriculitis affect cognition. These children are more prone to learning difficulties and seizure disorders. Early detection, correct diagnosis and prompt treatment of NTDs improve the outcome.

Long-term outcome studies have reported that 1-year survival rate is 87% which implies that about 78% all patients with MMC will live to the age of 17 years. There is an increased risk for lower limb weakness or paralysis, tethered cord, syringomyelia, bladder and bowel incontinence and orthopedic problems. Bowel incontinence is seen in 14% and urinary incontinence may be present in 25%. Renal dysfunction is an important cause of death.

PREVENTION

The currently accepted strategies are (a) antenatal screening for NTD with medical termination of affected pregnancy (b) folic acid supplementation and its role in both primary and secondary prevention.

Primary prevention Periconceptional folic acid supplementation **(Box 2)** is a simple and effective strategy that can prevent debilitating malformation and has brought down the incidence by 70%. Food fortification and improving the diet are other accepted methods. Strategies to add vitamin B_{12} and other nutrients such as zinc, vitamin A, myoinositol, etc. are being studied.

BOX 2 Prevention of neural tube defects: periconceptional folic acid supplementation

Indication 1: All prospective mothers
- *Dose:* 0.4 mg/day
- *When:* 2 months prior to conception and 3 months after conception

Indication 2: Prospective mothers with previous child with NTD
- Dose: 4 mg/day
- *When:* 2 months prior to conception and 3 months after conception

Note: For prospective mothers taking AEDs, folic acid–dose and duration as in Indication 2. Effectiveness is controversial.

Secondary prevention Family counseling is extremely vital when there is an affected child because recurrence risk is 4% after one affected child, 10% after two affected children. MTHFR polymorphisms should be studied in multiple recurrences of NTD. Prenatal screening and termination of the affected pregnancy prevents birth of babies with NTDs and periconceptional folic acid in subsequent pregnancies is advised.

IN A NUTSHELL

1. Neural tube defects are one of the most common congenital anomalies of the CNS.
2. Failure of spontaneous closure of the neural tube is responsible for most neural tube defects.
3. The common NTDs are spina bifida occulta, meningocele, MMC, anencephaly and encephalocele.
4. The inheritance is multifactorial as a result of genetic and numerous environmental factors.
5. The clinical presentation consists of the spinal lesion accompanied by weakness or paralysis of lower limbs, bladder and bowel dysfunction and orthopedic problems.
6. Complications of NTDs are meningitis, hydrocephalus due to Chiari II malformation, renal failure and hydronephrosis.
7. Antenatal diagnosis is possible with maternal and amniotic fluid AFP, ACH and fetal imaging.
8. Treatment consists of parental counseling, medical and surgical management such as repair of NTD and shunting.
9. *Prevention:* Periconceptional folic acid has brought down the occurrence by 70%.
10. The extent and involvement of the nervous tissue decides the severity and the outcome.

MORE ON THIS TOPIC

Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364:993-1004.

Bhide P, Sagoo GS, Moorthie S, et al. Systematic review of birth prevalence of neural tube defects in India. Birth Defects Res A Clin Mol Teratol. 2013;97:437-43.

Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least developed area of India: a population-based study. Lancet. 2005;366:930-31.

Godbole K, Deshmukh U, Yajnik C. Nutri-genetic determinants of neural tube defects in India. Indian Pediatr. 2009;46:467-75.

Gupta H, Gupta P. Neural tube defects and folic acid. Indian Pediatr. 2004;41:577-86.

Phadke S, Aggarwal M. Neural tube defects: A need for population-based prevention program. Indian J Hum Genet. 2012;18:145-7.

Ratan SK, Rattan KN, Pandey RM, et al. Evaluation of the levels of folate, vitamin B_{12}, homocysteine and fluoride in the parents and the affected neonates with neural tube defects and their matched controls. Pediatr Surg Int. 2008;24:803-8.

Sandler AD. Children with spina bifida: key clinical issues. Pediatr Clin North Am. 2010;57:879-92.

Chapter 42.5
Brain Malformations
Jatinder S Goraya

Brain malformations (BM) are the structural abnormalities of the brain that result from defects during early stages of embryological development of the brain. Given the complex nature and wide range of functions of the brain, brain malformations can result in myriad symptoms and signs in the affected child. Brain development is under the influence of several genetic factors, and genetic basis of many of the commonly known brain malformations has been elucidated and defective genes identified facilitating the genetic diagnosis and counseling.

EPIDEMIOLOGY

Advent of neuroimaging techniques especially the magnetic resonance imaging (MRI) resulted in the increased recognition of brain malformations. Brain malformations have been estimated to occur with an incidence of approximately 3.32/1,000 and the prevalence of approximately 2.21/1,000. The incidence and prevalence of the individual brain malformation is described under the specific malformations below. Data from developing countries is not available.

CLASSIFICATION

The classification of brain malformations continues to evolve as advances in genetics and neuroimaging add new information. Classification of malformations of brain on embryological and anatomical basis is easy to understand and follow **(Table 1)**. Classification systems based on underlying molecular or genetic defects are too complex and beyond the scope of this chapter.

EMBRYOLOGICAL CONSIDERATIONS

At the end of primary neurulation, the rostral end of the neural tube organizes to form three primary vesicles: (1) the hindbrain (rhombencephalon), (2) the midbrain (mesencephalon) and (3) the forebrain (prosencephalon). Soon three flexures (bends) make their appearance—the mesencephalic flexure at the midbrain level, the cervical flexure at the junction of hindbrain with spinal cord and the pontine flexure in the hindbrain. The forebrain divides and develops into telencephalon, and the diencephalon from

Table 1 Classification of brain malformations

- Disorders of forebrain development
  - Holoprosencephaly
  - Agenesis of corpus callosum
  - Septo-optic dysplasia
  - Septum cavum pellucidum
- Disorders of cerebellum and brainstem development
  - Chiari 1 malformation
  - Joubert syndrome and related disorders
  - Dandy-Walker malformation
  - Pontocerebellar hypoplasia
  - Isolated brainstem abnormalities
- Malformations of cortical development
  - Lissencephaly and subcortical band heterotopias
  - Nodular heterotopias
  - Polymicrogyria
  - Schizencephaly
  - Focal cortical dysplasias

which optic vesicles arise bilaterally. The cerebral hemispheres develop from telencephalon, and expand to completely cover the diencephalon. The hindbrain divides into rostral metencephalon from which the pons and the cerebellum develop, and caudal part becomes myelencephalon which eventually become medulla oblongata. The mesencephalon develops into midbrain.

ETIOLOGY

Genetics plays a major role in the causation of various brain malformations. Both autosomal and X-linked forms of brain malformations have been reported. Specific gene defects have been identified and clinically exploited for diagnostic purposes (see individual brain malformations vide infra). Sporadic occurrence as well as chromosomal imbalance may account for some forms of brain malformations. In addition, brain malformations may be associated with certain inborn errors of metabolism such as nonketotic hyperglycinemia (agenesis of corpus callosum), Zellweger syndrome (polymicrogyria), glutaric aciduria type 2 (cerebellar vermis hypoplasia) and disorders of glycosylation (pontocerebellar hypoplasia). Some congenital malformations syndromes such as Smith-Lemli-Opitz syndrome, Miller-Dieker syndrome, Rubinstein-Taybi syndrome, etc. also have associated brain malformations. Exposure to environmental factors such as ionizing radiation, therapeutic drugs, intrauterine infections such as cytomegalovirus are known to cause certain types of brain malformations.

CLINICAL FEATURES

Wide range of clinical manifestations can be seen as a consequence of underlying brain malformation. The age of onset varies from birth (in some cases may be intrauterine) to adulthood depending upon the severity and complexity of the brain malformations. Neonatal seizures including refractory epileptic encephalopathies, hypotonia, feeding or breathing difficulties tend to be the earliest manifestations. During infancy and early childhood, developmental delay, seizures, including infantile spasms, partial seizures and other refractory epilepsy syndromes such as Lennox-Gestaut syndrome may unmask the underlying brain malformations. Intellectual disability, developmental language disorders, specific learning difficulties, behavioral disability, epilepsy, motor difficulties secondary to spasticity, ataxia, weakness or movement disorder become evident as the children grow old. Special sensory deficits such as blindness may be encountered. Although all these function deficits are not specific for brain malformations, certain phenotypical characteristics may point to a specific brain malformation. For example, occurrence of infantile spasms in a female infant with retinal lacunae points to Aicardi syndrome. Zellweger syndrome has characteristic facies which helps in the diagnosis. Brain malformations are also increasingly being diagnosed during routine or dedicated prenatal ultrasonographic examinations. Signs and symptoms that are relatively specific for certain brain malformations are discussed under individual malformations of the brain.

DIFFERENTIAL DIAGNOSIS

As mentioned above, clinical presentation of brain malformations can be simulated by several congenital syndromes without identifiable brain malformations as well as by acquired neurological disorders. The diagnosis of brain malformations should be suspected in any infant with early onset neurological symptoms such as developmental delay, seizures or hypotonia in the absence of known metabolic derangements such as electrolyte

imbalance, hypoglycemia or hypocalcemia and infectious etiology. Though neuroimaging has rendered the diagnosis of common brain malformations rather easy, it requires the expertise of an experienced neuroradiologist to detect subtle alterations in the brain anatomy that is often seen with focal cortical dysplasia (FCD), heterotopias and polymicrogyria. Neuroimaging with magnetic resonance provides anatomical diagnosis of specific malformation in most of the cases with its ability to see brain in various planes, though further evaluation especially genetic may sometimes be required to reach a final diagnosis and for genetic counseling.

TREATMENT

As a rule, brain malformations do not have any specific treatment. Treatment is largely symptomatic and multidisciplinary. Antiepileptic medications are used for control of seizures. Seizures tend to be refractory frequently and polypharmacy is not uncommon. Drugs are also sometimes needed to treat spasticity, sialorrhea and movement disorders. Physical, occupational and speech therapy are generally required as patients frequently manifest cerebral palsy, speech and swallowing difficulties. Orthopedic, neurosurgical, ophthalmological consultations are needed in appropriate cases. Genetic diagnosis and counseling is important where such facilities are available. Risk of recurrence and possibility of prenatal diagnosis should be communicated to prevent the birth of another affected child after the diagnosis of brain malformation in an index case.

The outcome in brain malformations depends upon the underlying malformation. Severe and diffuse malformations tend to have grave prognosis for development, seizure control, and survival.

SPECIFIC BRAIN MALFORMATIONS

Holoprosencephaly

This brain malformation results from failure of the forebrain or prosencephalon to divide in the midline into two distinct cerebral hemispheres. Midline facial defects are frequently seen. This is the most common developmental anomaly of the forebrain. It occurs in 1 in 250 pregnancies but only in 1 in 10,000 live births as majority of the affected fetuses do not survive till delivery.

Holoprosencephaly (HPE) is classified according to the degree of separation of the cerebral hemispheres: Alobar, semilobar, lobar and a midline interhemispheric variant. In addition to nonseparation of the cerebral hemispheres, there is variable degree of nonseparation of hypothalamic, thalamic, lentiform and caudate nuclei. The alobar holoprosencephaly is the most severe, showing almost complete absence of separation of the cerebral hemispheres with characteristic midline single ventricle (a crescent-shaped monoventricle) which may communicate with a dorsal cyst. The corpus callosum, falx cerebri and interhemispheric fissure are absent as are the olfactory bulbs and tracts. Third ventricle is absent owing to nonseparation of thalami and hypothalami. In the semilobar HPE, an intermediate form of HPE, separation of the cerebral hemispheres is restricted to the posterior part and is absent anteriorly. As an accompaniment, corpus callosum shows absence of genu and body and only splenium is present posteriorly. The frontal horns of lateral ventricle are absent and only occipital horns and trigones are present. Septum pellucidum is absent and third ventricle tends to be small due to partial separation of deep gray nuclei. Lobar HPE is the mildest form, and here the lack of separation is restricted to the most rostral and ventral parts of the cerebral hemispheres. Rudimentary frontal horns may be present and only genu of corpus callosum is absent. In the midline interhemispheric variant (syntelencephaly), cerebral hemispheres show lack of separation across the midline affecting the posterior frontal and parietal lobes with absent corpus callosum in the corresponding region. Anterior frontal lobes, basal forebrain and occipital lobes are normally separated. HPE severity varies across a spectrum and classification of an affected patient into a specific subtype may not be possible. With the advent of advanced neuroimaging techniques, milder forms are being increasingly recognized.

Both environmental and genetic factors may be associated with the causation of HPE. Maternal diabetes, fetal exposure to alcohol and retinoic acid have the strongest association. Other reported risk factors such as hypocholesteremia, viruses, toxins and medications have also been reported. HPE can also be seen with chromosomal abnormalities such as trisomy 13 or 18, congenital malformation syndromes such as Smith-Lemli-Opitz syndrome, Rubinstein-Taybi syndrome and Pallister-Hall syndrome. HPE occurring as a single gene disorder in the form of autosomal dominant and autosomal recessive forms has been described. Several genes namely sonic hedgehog (SHH**)**, *ZIC2* (ZIC family member 2 or *zinc finger protein of the cerebellum* 2), *SIX3* (SIX homeobox 3) and transforming growth factor beta (TGFB induced factor (TGIF) have been associated with the occurrence of HPE.

Clinically, midline facial anomalies frequently accompany HPE. Facial midline abnormalities include hypotelorism, flattened nasal bridge, median cleft lip and palate, or a single median maxillary central incisor. Cyclopia, with the presence of a single median eye and a proboscis, can be present. Presence of normal facies is, however, not unusual. Other children with HPE come to attention through the occurrence of variable degree of developmental delay, tone abnormalities, and epilepsy with partial or generalized seizures. Feeding and swallowing difficulties are also very common. Patients tend to have microcephaly in the absence of hydrocephalus which may complicate the clinical course in some children. Endocrinopathies are common due to hypothalamic involvement and especially frequent is the diabetes insipidus. Growth hormone deficiency, hypocortisolism, and hypoparathyroidism may be seen less commonly. Generally, severity of clinical manifestations is commensurate with the severity of HPE. Diagnosis is by MRI.

No specific treatment is available and management is largely symptomatic. Epilepsy, spasticity and dystonia require appropriate medication. Special attention need to be paid to the feeding and swallowing dysfunction to prevent malnutrition and may require gastrostomy tube. Diabetes insipidus and other endocrinopathies need early detection and intervention. Surgical treatment for hydrocephalus or spasticity may be needed. The morbidity and mortality in HPE varies with the severity of the disease. Longer survival is common with milder form. Causes of death include aspiration pneumonia, severe dehydration from diabetes insipidus and rarely intractable epilepsy.

Prenatal diagnosis can be achieved through a combination of prenatal ultrasonography, fetal MRI and gene testing. The risk of recurrence is about 6% in isolated HPE. In familial cases where causative gene has been identified, prenatal diagnosis is through genetic testing by means of amniocentesis or chorionic villous biopsy.

Agenesis of Corpus Callosum

Corpus callosum is the largest white matter tract in the brain connecting the two cerebral hemispheres and providing the pathway for communication between them. It develops between the 8th week and 14th week of fetal life and the axons that traverse it connect the homotopic regions of the cerebral hemispheres. Agenesis of the corpus callosum (ACC) is the most common brain malformation found in 1 in 3,000 livebirths.

Agenesis of corpus callosum can be partial or complete. It can occur as an isolated entity or more commonly associated with other malformations of brain or cortical development. Some patients have abnormalities in organ systems outside central nervous system commonly affecting renal, musculoskeletal or ophthalmological structures and defining specific genetic/malformation syndromes.

Genetic factors play major role in the causation of ACC. Increased maternal or paternal age is associated with higher risk of occurrence of ACC. Chromosomal aberrations have been identified in a significant number of patients with ACC. There is large list of single gene disorders as well as congenital malformation syndromes associated with ACC. Certain inborn errors of metabolism such as pyruvate dehydrogenase deficiency, nonketotic hyperglycinemia and pyruvate decarboxylase deficiency have ACC as a part of the clinical spectrum. Of the environmental factors, alcohol consumption by mothers during pregnancy is associated with occurrence of ACC (fetal alcohol syndrome).

Clinically, a wide range of clinical manifestations can be seen with ACC and the onset of symptoms can be during infancy to late childhood. ACC can rarely be asymptomatic. Commonly ACC is associated with developmental delays, mental retardation, epilepsy or cerebral palsy. Deficits in cognitive, social and behavior domains, autism and attention deficit hyperactivity disorder (ADHD) has increased prevalence in children with ACC. Children with additional brain malformations (neuronal heterotopias, PMG, etc.) tend to have more severe neurological dysfunction. Some manifestations related to extraneurological involvement may be seen. Children with ACC as part of congenital malformation syndromes have specific dysmorphism suggesting the syndromal diagnosis. The diagnosis of ACC is made by MRI **(Fig. 1)**. ACC may also be detected inutero during the ultrasonographic examination.

Treatment is symptomatic.

Septo-optic Dysplasia

This is a rare brain developmental defect comprising optic nerve hypoplasia, pituitary abnormalities and absent septum pellucidum. Etiologically young maternal age is a risk factor. Fetal exposure to alcohol, smoking, cocaine and certain other toxins or drugs may be associated with increased risk of occurrence of septo-optic dysplasia (SOD). Two genes namely *HESX1* (homeobox, ES cell expressed 1) and *SOX2* (sex determining region Y—BOX 2) have been found in association with SOD.

Figure 1 T1-weighted saggital magnetic resonance (MR) image showing complete absence of corpus callosum. The sulci and gyri on the medial surface appear radiating from the third ventricle

Clinically, the children may come to attention at birth manifesting hypoglycemia secondary to pituitary insufficiency, and are found to have microphallus, undescended testes, and midline birth defects such as cleft lip or palate. Ophthalmological and neuroradiological examination with MRI reveals characteristic findings. Patients with SOD are also prone to other pituitary hormone deficiencies such as adrenocortical hormone, growth hormone, gonadotropic hormone and thyroid stimulating hormone. Many patients have addition brain malformations which may account for occurrence of seizures, developmental delay or cerebral palsy in the affected children.

Treatment of neurological manifestation of SOD is largely symptomatic. Particular attention needs to be given to endocrinological evaluation, treatment and monitoring. Ophthalmological examination and follow-up is necessary.

Disorders of Brainstem and Cerebellar Development

These disorders will be considered together because of co-occurrence of abnormalities of brainstem in patients with cerebellar developmental defects and vice-versa.

Chiari 1 malformation This anomaly refers to the downward displacement of cerebral tonsils of at least 3–5 mm through foramen magnum into the spinal canal. The reasons for downward herniations are not clear through several theories such as traction by tethered cord, and small posterior fossa has been proposed. No clear etiological factor can be identified in majority of the patients.

Clinically, patients may be entirely asymptomatic coming to attention through neuroimaging done for some other purposes. Those who are symptomatic frequently manifest posterior headache that is increased with Valsalva maneuvers. The pain may radiate anteriorly to vertex or downward to neck and shoulders. Compression of brainstem and spinal cord may occur manifesting with long tract signs such as spasticity, hyper-reflexia, urinary incontinence, ataxia or sensory changes. Presentation may be complicated by the development of syringomyelia in some patients.

Treatment where indicated is surgical decompression of the posterior fossa and duraplasty. Milder cases without syringomyelia and those who have displacement of tonsils less than 3 mm may be observed conservatively as spontaneous improvements are known.

Dandy-Walker malformation (DWM) Disturbed anatomy of DWM includes hypoplasia and upward rotation of the cerebellar vermis, cystic dilatation of the fourth ventricle, and an enlarged posterior fossa with upward displacement of the lateral sinuses, tentorium and torcular herophili.

Dandy-Walker malformation can be caused by chromosomal aberrations, often forming the part of presentation of the congenital malformation syndromes such as Axenfeld-Rieger syndrome. Deletions of *ZIC1* (ZIC family member 1 or *zinc finger protein of the cerebellum 1*), *ZIC4* (ZIC family member 4 or *zinc finger protein of the cerebellum 4*), and *FOXC1* (forkhead box C1) genes can also result in DWM.

Clinically the affected persons may be asymptomatic especially when DWM is unassociated with other malformations of the brain. Others present with variable cognitive, language or motors delays. Hydrocephalus can occur as a complication requiring place-ment of a ventriculoperitoneal shunt. Extracranial organ system involvement affecting heart, urogenital tract, gut and limbs occur frequently in patients affected by DWM.

Treatment is largely symptomatic. Hydrocephalus requires shunt placement.

Joubert syndrome (JS) Joubert syndrome and related disorders are the most common inherited congenital malformation of the

cerebellum. The cerebellar malformation includes cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and abnormally deep interpeduncular fossa which together produce a characteristic molar tooth sign on brain imaging. These conditions have been described in the chapter on Ataxia.

Malformations of Cortical Development

Development of human cerebral cortex occurs between the 8th week and 24th week of gestation and can be divided into three steps—(1) the neural stem cell proliferation and differentiation, (2) neural migration and (3) cortical organization. Neural stem cell proliferation and differentiation (neurogenesis) begins in the ventricular zone giving rise to cells that will eventually migrate outward to become cortical neurons. The neural migration is guided by the network of axons of radial glial cells under the influence of protein molecules regulated by several genes. The cortical organization involves formation of six-layers of cortical ribbon, formation of sulci and gyri, axon myelination, and synaptic proliferation and pruning. Disruption of any of these processes can result into malformations of cortical development (MCD).

Lissencephaly (LIS)

Lissencephaly, or *smooth brain*, is the result of disruption of the neural migration leading to the formation of abnormally thick cortex and an abnormal gyral pattern in the form of absence of gyral formation (agyria) or the presence of abnormally wide gyri (pachygyria). The thick cortex in LIS is abnormal and consists of four abnormal layers including the deep zone of diffuse neuronal heterotopias. The underlying ventricles are enlarged and dysplastic. Subcortical band heterotopias (SBH) is a related disorder, in which symmetric and circumferential bands of gray matter are located in the subcortical white matter just underneath the cortex and separated from it by a thin band of white matter. The overlying cortex may be normal or mildly immature. The term, *double cortex* has been used to describe the malformation.

Several types of LIS have been described. In most common or classic form, the cortex is four-layered and 12–20 mm thick. The malformation may be diffuse or more severe in anterior (*Lissencephaly 1* or *LIS1* gene) or posterior (Doublecortin or *DCX* gene) head regions. Miller-Dieker syndrome is a form of classical LIS caused by deletion of 17p13.3 and affected children have characteristic facies. The LIS in this disorder has no anterior or posterior dominance. Rare three-layered (X-linked lissencephaly with abnormal genitalia caused by mutations in Aristaless related homeobox gene or *ARX* gene), and two-layered (complete agyria with severe brainstem and cerebellar hypoplasia) forms of LIS have been described.

Clinically children with most common type of LIS are asymptomatic during newborn period. Neurological dysfunction becomes obvious during infancy with developmental delay, poor feeding or tone abnormalities. More commonly seizures bring the affected infants to medical attention. Infantile spasms are the most common type of epilepsy and may later evolve into Lennox-Gestaut syndrome and other forms of seizure may occur. Epilepsy is usually refractory. In some rare forms of LIS, other manifestations such as abnormal genitalia, dysmorphism, etc. may be obvious on clinical examination.

Diagnosis is made by neuroimaging **(Fig. 2)**. Magnetic resonance where available is the modality of choice to diagnose and classify the lissencephaly as well as to detect additional associated brain malformations. Neuroimaging allows the differentiation of various types of LIS as well as the pattern and the severity of the malformations. This coupled with specific clinical characteristics such as dysmorphism, severe microcephaly, abnormal genitalia allows for syndrome diagnosis and helps in directing the appropriate genetic evaluation. Several genes *ARX,*
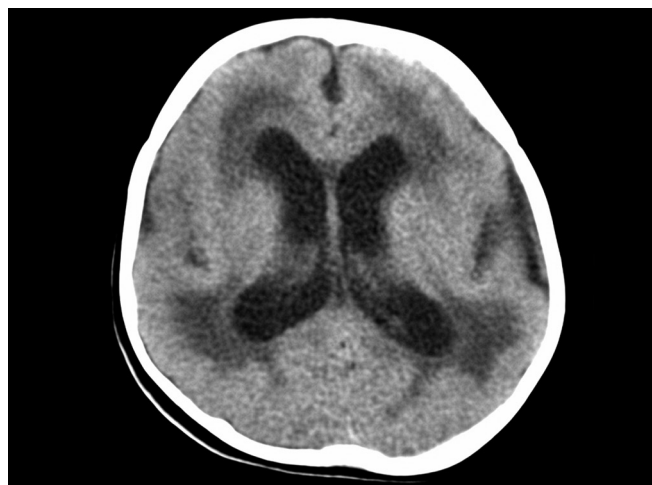
Figure 2 CT head of a child with lissencephaly showing smooth and thickened cortex. Underlying white matter is abnormally hypodense and ventricles dilatation is apparent
Source: Dr Chandan Kakkar.

DCX, LIS1, RELN (reelin), and *TUBA1A* (Tubulin, alpha 1a) have been recognized to be associated with various types of LIS and are available for clinical testing.

Treatment is generally symptomatic. Since epilepsy is the dominant feature, antiepileptic medications tailored to the specific seizures and epilepsy type are required for effective seizure control.

Cobblestone Malformation

Previously called Lissencephaly type 2, cobblestone malformation or lissencephaly is a severe brain malformation associated with abnormal migration from the brain into the leptomeninges, and frequently with eye anomalies and congenital muscular dystrophy. Cobblestone malformation is characteristically associated with Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain disease (MEB) and Walker-Warburg syndrome (WWS).

The brain malformation consists of poor gyral development, cerebral and cerebellar cortical dysplasia, hydrocephalus, brainstem hypoplasia with dysplasia of the inferior olives and dentate nuclei, and hypoplasia of the corticospinal tracts in brainstem and spinal cord. The malformation is the result of defective glycosylation of α-dystroglycan.

These children present with developmental delay, hypotonia, weakness and poor vision. Children with WWS have the severest phenotype followed by MEB and FCMD. These syndromes are inherited in autosomal recessive pattern. Genetic diagnoses through testing for *POMT1* (Protein-O-Mannosyltransferase 1), *POMT2* (Protein-O-Mannosyltransferase 2), *POMGnT1* (Protein O-Linked Mannose N-Acetylglucosaminyltransferase 1), *FKRP* (fukutin-related protein), *FKTN* (fukutin) and *LARGE* (like-glycosyltransferase) is possible and may be needed for genetic counseling and prenatal diagnosis.

Neuronal Heterotopia (NH)

Neuronal heterotopia is diagnosed when masses of gray matter are identified at an abnormal location in the brain and results from arrested neural migration. Two common types include periventricular nodular heterotopia (PNH) and subcortical nodular heterotopias.

In PNH nodular masses of neurons are seen to line the ventricular surface and protrude into the ventricular lumen giving it an uneven appearance **(Fig. 3)**. There may be a single or multiple nodules occurring in symmetric or asymmetric pattern.
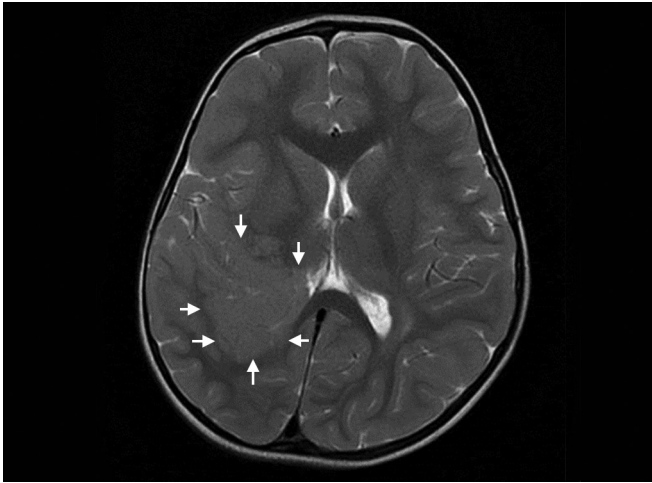
Figure 3 MRI brain of a child with nodular heterotopia. There is large nodular mass of gray matter in the white matter of posterior quadrant of right cerebral hemisphere (arrows). The lesion is extending into the lumen of right occipital horn of lateral ventricle
Source: Dr Chandan Kakkar.

Figure 4 MRI brain showing polymicrogyria (multiple small and shallow gyri) in the right fronto-parietal cortex. There is dilatation of the overlying subarachnoid space
Source: Dr Chandan Kakkar.

They may occur as an isolated entity or be associated with other brain malformations. Subcortical nodular heterotopias occur in subcortical location as a large mass of heterotopic neurons expanding the affected cerebral hemisphere.

Epilepsy, usually partial is the most common feature of NH. The onset is variable but may not to occur during infancy or childhood. Mild cognitive deficits and learning difficulties may be encountered. Clinical picture, however, may be altered by associated brain malformations resulting in severe phenotype with microcephaly, mental retardation or refractory epilepsy.

Diagnosis is made on neuroimaging. *FLNA* (*filamin A alpha*) gene mutations may be identified in some families with classic X-linked PNH.

Polymicrogyria

Polymicrogyria is characterized by the presence of multiple small shallow gyri which may or may not be visible macroscopically. It can occur unilaterally; when bilateral can be symmetric or asymmetric. The perisylvian cortex is most commonly involved brain region. PMG mostly occurs as an isolated abnormality but can be associated with other abnormalities of brain development. Intrauterine vascular insult, fetal infections with cytomegalovirus, metabolic diseases such as peroxisomal and mitochondrial disorders, chromosomal abnormalities and multiple congenital anomaly syndromes may be associated with PMG.

Clinically, variable phenotype may occur in PMG. In bilateral perisylvian PMG, patients typically present with oro-lingual-facial dysfunction and epilepsy which together constitute what is called, *"congenital bilateral perisylvian syndrome"*. The oro-lingual-facial dysfunction is caused by the motor dysregulation affecting tongue, oral and facial musculature and results in difficulties with speech, sucking and swallowing, drooling and facial diplegia (pseuobulbar palsy). Epilepsy is common and multiple types of seizures—partial, atonic, tonic, generalized tonic clonic and atypical absences can occur and may become refractory. Continuous spike and wave discharges during slow sleep are frequently associated with PMG.

Brain imaging with MR (1.5T or more) is necessary to diagnose PMG and differentiate from other MCDs with which it may be easily confused **(Fig. 4)**. Cortex in PMG is usually mildly thickened with an irregular gray-white matter junction.

Treatment of PMG is symptomatic.
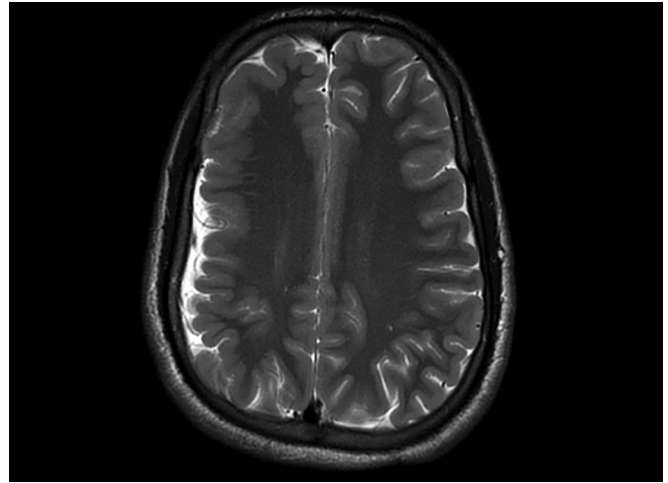
Schizencephaly (SCH)

Schizencephaly or *cleft brain* is now considered as a subtype of PMG. The cleft is full-thickness extending from the ventricular surface to the subarachnoid space and is lined by PMG. The cleft can be unilateral or bilateral, *open-lip* or *closed-lip*. In open-lip SCH, the walls of cleft do not appose. In closed-lip SCH, the walls of the cleft are apposed and may be fused together; a line of continuity between the lateral ventricle and subarachnoid space may, however, be visible. PMG most often occurs as an isolated abnormality but rarely may be associated with brain malformations.

Clinically, children with SCH present with hemiparesis, motor delays and seizures. Cognitive dysfunction occurs frequently.

Schizencephaly is readily diagnosed on brain MRI. Additional abnormalities, particularly the absence of septum pellucidum and hypoplastic optic nerves are detected in significant number of patients with SCH.

Focal Cortical Dysplasia

The term focal cortical dysplasia is used to describe a wide spectrum of cortical malformations associated with microscopic neuronal heterotopia, dyslamination, and abnormal cell types, namely, balloon cells and dysmorphic giant or cytomegalic neurons. It is the latter neurons that contribute to epileptogenesis. The extent of FCD is variable ranging from focal tranmantle, sublobar, lobar, posterior quadrantic, lobar and hemispheric. FCD are classified based on neuropathological criteria, detailed discussion of which is beyond the scope of this chapter (see MORE ON THIS TOPIC).

Magnetic resonance imaging is the modality of choice for diagnosis. Gross FCDs are easily detected as areas of cortical thickening, abnormal gyration, blurring of the gray-white junction, high signal at the base of the lesion and in the underlying white matter on T2 and fluid-attenuated inversion recovery (FLAIR) sequences. Some FCDs are so subtle that they may be missed even on high-quality imaging.

Most common clinical manifestation of FCD is epilepsy which can arise at any age from newborn period to adulthood. Intrauterine seizures may occur. Extensive FCDs may be associated with developmental, cognitive and motor deficits. Simple or complex partial seizures with or without secondary generalization,

and infantile spasms can occur depending upon the location of FCD and age of the child. Infantile spasms and refractory seizures may have deleterious effects on the neurodevelopment in a young child in the presence of even a small FCD. Some children with FCD have underlying tuberous sclerosis.

Treatment of FCD is centered on anti-epileptic medications due to the fact that seizures are the most common clinical manifestation. In children with refractory epilepsy, respective surgery may be curative but involves extensive presurgical evaluation by experts in epilepsy.

MORE ON THIS TOPIC

Blümke I, Thom M, Aronica E, et al. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011;52: 158-74.

Nissenkom A, Michelson M, Ben-Zeev B, Lerman-Sagie T. Inborn errors of metabolism: A cause of abnormal brain development. Neurology. 2001;56:1265-72.

Romani M, Micalizzi A, Valente E. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol. 2013;12:894-905.

Sarnat HB, Curatolo P. Handbook of clinical neurology: Malformations of nervous system. USA: Elsevier Saunders; 2008.

Swaiman KE, Ashwal S, Ferriero DM, Schor NF. Swaiman's Pediatric Neurology, Principles and Practice. USA: Elsevier Saunders; 2012.

Sztriha L, Spectrum of corpus callosum agenesis. Pediatr Neurol. 2005;32: 94-105.

IN A NUTSHELL

1. Brain malformations are an important cause of neurological dysfunction in children.
2. Both genetic and environmental factors are important in the causation of brain malformations.
3. Brain malformations are frequently associated with developmental delay/intellectual disability, epilepsy, behavioral problems and motor difficulties.
4. Brain malformations are readily diagnosed with neuroimaging with MRI.
5. Genetic diagnosis through identification of affected genes is possible and should be done where available.
6. Affected family should be offered genetic counseling and prenatal diagnosis.

Chapter 42.6
Neurocutaneous Disorders
Maya Thomas, Renu George, Karthik Muthusamy

Neurocutaneous disorders, (also referred to as Phakomatoses earlier, origin from the Greek word phakos, meaning *mother spot* or birthmark) include a diverse group of disorders with predominant involvement of the skin and central nervous system tissues, owing to their common origin from the ectoderm. They are now believed to be disorders of neural crest tissue and are also called neurocristopathies. The disorders that are categorized under neurocristopathies include tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), epidermal nevus syndrome, neurocutaneous melanocytosis, incontinentia pigmenti and hypomelanosis of Ito. Additional disorders that are considered under phakomatosis are SWS, von Hippel-Lindau syndrome, ataxia telangiectasia, to mention a few. It is important to recognize and be familiar with these skin lesions as they provide a clue to the underlying neurological disorder. Four major disorders will be discussed and the salient features of the rest will be represented in a tabular form.

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex is a disorder that can affect multiple organ systems of varying severity and hence has differing clinical expression. It is also called Bourneville disease, after Desire-Magloire Bourneville who is credited with the first detailed description of the cerebral lesions. Birth incidence is estimated to be 1 in 5,800 livebirths.

Etiology
It is an autosomal dominant disorder with complete penetrance but variable expressivity. Only one-third of cases are inherited, the rest are sporadic and occur due to spontaneous mutation. Current molecular diagnostic methods detect mutation in either the TSC1 or TSC2 gene in 85% of TSC patients, both inherited and sporadic. Mutations in TSC2 are five times more common in sporadic cases whereas in the inherited cases, the proportion of mutations in TSC1 and TSC2 are equal.

Pathogenesis
TSC1 gene on chromosome 9q34 encodes hamartin and TSC2 gene on chromosome 16p13.3 encodes tuberin. Hamartin and tuberin complex normally work together and through a cascade of downstream reactions stimulate protein translation, cell growth, and proliferation. The complex inhibit the GTPase Ras homolog enriched in brain (RHEB) which in turn is responsible for activating an important intracellular regulator of cell growth and metabolism known as mammalian target of rapamycin complex 1(mTORC1). Thus, mutations of hamartin or tuberin in TSC lead to hyperactivation of the downstream mTOR pathway resulting in unchecked cell growth and proliferation. This has led to the use of mTORC1 inhibitors like sirolimus and everolimus for the treatment of several clinical manifestations of TSC like cerebral subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomas. Rapamycin, which is also a drug used in TSC makes the dysregulated mTOR pathway return to normal in cells that lack TSC1 or TSC2.

The brain lesions found in TSC, include cortical tubers, subependymal nodules, and SEGA. Heterotopic neurons are commonly scattered in the deep white matter. Cortical tubers are characterized by proliferation of glial and neuronal cells, and loss of the six-layered structure of the cortex.

Clinical Features
The clinical features of TSC depend on the location of the tubers which are predominantly located in the brain, skin, eyes, heart, kidneys and lungs.

Neurological Manifestations
Seizures are the most common presenting symptom in TSC, manifesting in up to 85% of patients. Seizures usually have their onset in the first year of life and type of seizures include infantile spasms or focal seizures like unilateral tonic or clonic seizures, tonic eye deviation or head turning. Seizures may increase in frequency and severity with poor response to antiepileptic medications. Prompt seizure control is important and can prevent development of an epileptic encephalopathy and improve cognitive outcome. Unfavorable prognostic factors include onset of seizures in infancy, multiple seizures types, multifocal spikes on EEG and occurrence of new electroencephalographic (EEG) foci during evolution. Cortical tubers act as epileptic foci and epileptogenesis within these dysplastic neurons is caused by diminished neuronal inhibition, secondary to molecular changes of γ-aminobutyric acid (GABA) receptors, and enhanced excitation, which is secondary to molecular changes of glutamate receptors. Vigabatrin, an inhibitor of GABA transaminase, through this mechanism can control spasms in up to 95% of children.

Tuberous sclerosis complex-associated neuropsychiatric disorders (TAND) is associated with cognitive and behavioral manifestations like profound cognitive impairment in about 30% of individuals. This includes attention-deficit/hyperactivity disorder (ADHD) and autistic spectrum disorder. More than 50% have average intelligence but could have specific impairments in memory, attention or executive skills. The risk for developing autism includes early onset infantile spasms with EEG changes, tubers in the temporal lobe and a mutation in the TSC2 gene.

In about 10% of cases the subependymal nodules transform slowly into SEGAs which are of mixed glia-neuronal lineage. Growth of these lesions at the foramen of Monro can block circulation of the cerebrospinal fluid (CSF), leading to progressive lateral ventricular dilatation and increased intracranial pressure.

Cutaneous Manifestations
Cutaneous lesions are seen in up to 96% of patients with TSC, the most common being facial angiofibroma, also called as adenoma sebaceum. These are pink or red papules that appear between 1 year and 4 years of age in a butterfly distribution over the nose and cheeks **(Fig. 1)**. The lesions increase in number and size through adolescence. Other lesions include hypomelanotic macules known as ash leaf macules **(Fig. 2)**, gingival fibromas, Shagreen patch which are thickened, firm areas of subcutaneous tissue often at the lower back **(Fig. 3)**, and fibrous plaques on forehead and face **(Fig. 4)**.

Other Manifestations
Renal manifestations of TSC are the third most common clinical feature. The lesions seen are angiomyolipomas, isolated renal cyst, autosomal dominant polycystic kidney disease (PKD), and renal cell carcinoma. Angiomyolipomas observed in as many as 80% of individuals with TSC, may be detected in childhood after the third year of age, or in adults. They are usually picked up incidentally but can also cause nonspecific flank pain. The angiolipomas potentially carry a risk of life-threatening hemorrhage from rupture of the dysplastic feeding blood vessel.

Figure 1 Adenoma sebaceum, papular lesions in a butterfly distribution over the nose and cheeks
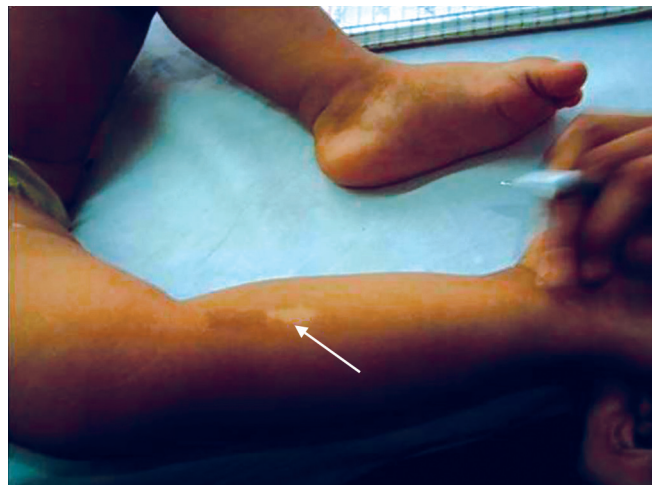
Figure 2 Hypomelanotic macule or ash leaf macule (arrow) over the leg seen in an infant who presented with infantile spasms

Figure 3 Shagreen patch (arrow) seen over low back are firm areas of subcutaneous tissue

Figure 4 Fibrous plaque on face

Cardiac involvement is usually in the form of rhabdomyomas, seen in 50–60% of patients with TSC. They are benign tumors which develop during intrauterine life and usually undergo spontaneous regression in the first few years of life. They produce symptoms predominantly through outflow tract obstruction, interference with valvular function or they can disrupt electrical conductivity and cause arrhythmias.

Ophthalmic manifestation is mainly in the form of retinal hamartomas present in about 50% of patients and can be found at any age. They appear as rounded, nodular, or lobulated areas on fundoscopic examination and cause no symptoms. Rarely, they affect visual acuity when it impinges on the fovea or optic nerve.

Pulmonary involvement occurs in three forms mainly in adult women and are symptomatic only in 1% of them. These are seen as multifocal micronodular pneumocytes hyperplasia, pulmonary cysts, and lymphangioleiomyomatosis (LAM).

Approach to Diagnosis

Cutaneous lesions of TSC are unmistakable and provide the single main clue to diagnosis. The diagnostic criteria are given in **Box 1**. Diagnosis is made when two major features, or one major and two minor ones are present. Genetic testing and counseling should be offered to individuals with TSC when they reach reproductive age and to first-degree relatives of affected individuals.

Management

Current management guidelines are based on the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Once a child is diagnosed with TSC, a complete baseline investigative work-up should be carried out to determine the extent of involvement of each of the organ system. This includes neuroimaging **(Fig. 5)**, ophthalmologic examination, echocardiogram and renal ultrasound. Electroencephalogram needs to be done in case of suspected seizures and when seizure occurrence is unclear such as in unexplained sleep disturbances; behavioral changes or when other alterations in cognitive or neurological function is present. Chest computed tomography is required in women during adulthood.

Epilepsy in TSC is treated with antiepileptic medication depending on the seizure type. Vigabatrin is especially effective in treating infantile spasms in TSC. Adrenocorticotropic hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. TAND requires comprehensive neuropsychological evaluation and appropriate treatment.

Cortical tubers and subependymal nodules require no treatment. SEGA, if asymptomatic may be left alone but require periodic neuroimaging to ensure there is no growth. Patients with large or growing SEGA, or with SEGA causing ventricular enlargement should undergo surgical resection and cerebrospinal fluid diversion.

Medical treatment with mTORC inhibitors may be used for growing but otherwise asymptomatic SEGA. If skin lesions are rapidly changing or disfiguring, they may be considered for excision, laser or topical application of mTOR inhibitors. Retinal lesions are left alone and re-evaluation is required only if any symptoms arise.

Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy.

Women who develop LAM with moderate to severe lung disease will require mTOR inhibitors. They may even be candidates for lung transplantation.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 was also known as von Recklinghausen's disease until the end of the 20th century after von Recklinghausen, who in the latter part of the 19th century described tumors arising from the endoneurium of peripheral nerves as *neurofibromas* in two patients. Currently neurofibromatosis includes at least three distinct disorders, referred to as NF1, NF2, and schwannomatosis. NF1 is the most common of the neurofibromatoses, affecting approximately 1 in 3,000 individuals worldwide.

Etiology

Neurofibromatosis type 1 is inherited as an autosomal dominant disorder that affects males and females and all ethnic groups equally. It occurs due to a mutation in NF1 gene localized to chromosome 17q11.2 and spans over 350 kb of genomic DNA.

Pathogenesis

The NF1 gene encodes for the NF1 protein called neurofibromin, which functions as a negative regulator of *Ras*. Loss of neurofibromin results in high levels of activated *Ras*. In many cell types, activated *Ras* is a potent driver of cell proliferation and may be sufficient for tumor formation. In glial cells through downstream intermediates *Ras* regulates cell growth through the Akt/mTOR pathway. Neurofibromin is also a positive regulator of intracellular cyclic adenosine monophosphate (cAMP) levels. Initial studies in Drosophila revealed that learning and memory defects in NF1 mutant flies reflect reduced cAMP generation. Understanding of these pathways has led to clinical trials for new therapeutic drugs.

Clinical Features

Neurofibromatosis type 1 principally affects the skin, bone and peripheral nervous system and is characterized by multiple café-au-lait spots (CLSs), although CLSs are not specific to NF1 alone.
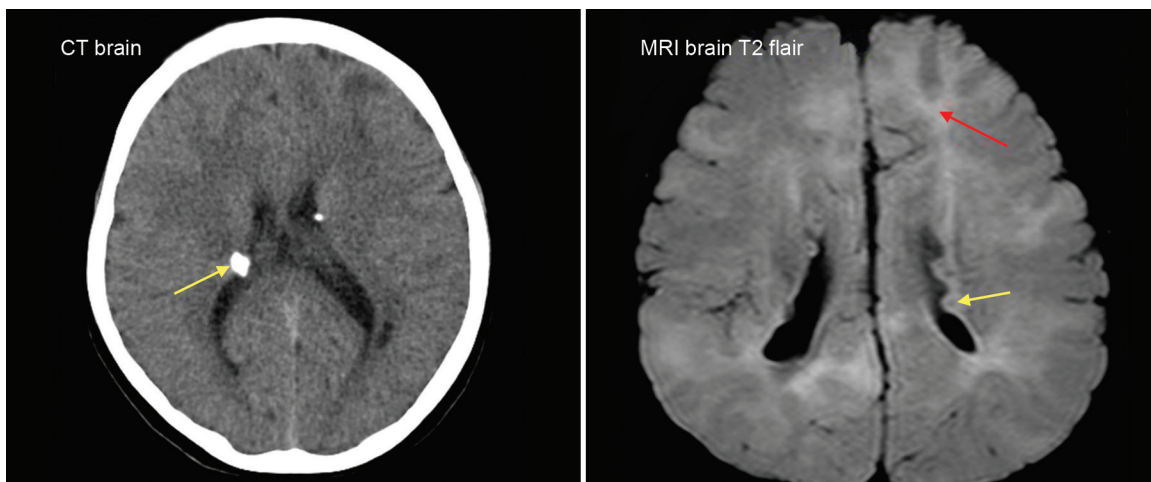
Figure 5   Plain CT brain showing calcified subependymal calcifications (arrow) and MRI brain T2 FLAIR axial image showing subependymal nodules (yellow arrow) seen as projections into the lateral ventricles and high signal intensities involving the cortex which represent cortical tubers (red arrow)

Café-au-lait macules are flat, pigmented spots that are usually visible in room light regardless of background skin pigmentation **(Fig. 6)**. Skinfold freckling **(Fig. 7)** is observed in 85% of NF1 individuals after age 3 years, and is noticeable in the axillae, groins, at the base of the neck, on the upper eyelids, and under the breasts. Neurofibromas **(Fig. 8)** are benign tumors that arise from Schwann cells and may occur anywhere in the body and involve a discrete region of an individual nerve. If it involves multiple nerve fascicles and extends over a length of a nerve and its branches, it is called plexiform neurofibroma. Neurofibromas increase in number after puberty.

Iris Lisch nodules are melanocytic hamartomas which are highly specific to NF1. They appear as dome-shaped pigmented hamartomas on the iris in late childhood, remain asymptomatic and require a slit-lamp examination to be visualized.

Optic glioma **(Figs 9A to C)** occurs in approximately 15% of individuals with NF1, usually beginning in the early years of life. The tumors seen in TSC are pilocytic astrocytomas that may involve the optic nerve, chiasm, and/or hypothalamus. Most are asymptomatic, but some may interfere with vision or cause hypothalamic disturbance such as precocious puberty, or other neurological symptoms.

Figure 6 Café-au-lait macule, hallmark of neurofibromatosis is a flat, hyperpigmented spot

Figure 7 Axillary freckling (Crowe sign), are clusters of concentrated melanin appearing as flat light brown macules

Figure 8 Cutaneous neurofibromas, are fleshy sessile skin lesions that arise from nerves in the skin

Skeletal dysplasia associated with NF1 includes long bone dysplasia and dysplasia of the sphenoid wing. Long bone dysplasia involving tibia is usually visible in early childhood as bowing of the leg. It may also involve other long bones like the fibula, radius, and ulna.

The final diagnostic criterion is the occurrence of a first-degree relative with NF1. Being an autosomal dominant disorder with complete penetrance and variable expression, many parents are first diagnosed when a child is referred for evaluation. Approximately 50% of affected individuals have no affected parent and represent new mutations of the NF1 gene. Some parents of sporadically affected children may have germline mosaicism, so recurrence is possible, though rare.

Complications seen in NF1 are listed in **Table 1**.

Approach to Diagnosis

Diagnostic criteria for NF1 are given in **Box 2**. Neuroimaging is warranted in the case of neurological manifestations. MRI T2 hyperintensities **(Fig. 9)** occur in the majority of NF1 children, particularly in the brainstem, cerebellum and basal ganglia, but also in the hippocampi, thalami, and cerebral hemispheres. They are thought to represent abnormal myelination and gliosis. Echocardiogram, computed tomography of the abdomen and chest are required only if there is clinical suspicion of underlying involvement.

Management

Management of NF1 currently consists of surveillance, surgical treatment of progressive lesions, and genetic counseling.

BOX 2 Diagnostic criteria for neurofibromatosis type 1

NF1 is diagnosed in an individual fulfilling two or more of these criteria:

- Six or more café-au-lait spots measuring at least 5 mm before puberty or 15 mm after puberty
- Skin-fold freckling
- Two or more neurofibromas or one plexiform neurofibroma
- Two or more iris Lisch nodules
- Optic glioma
- Characteristic skeletal dysplasia (long bone or sphenoid wing)
- Affected first-degree relative.
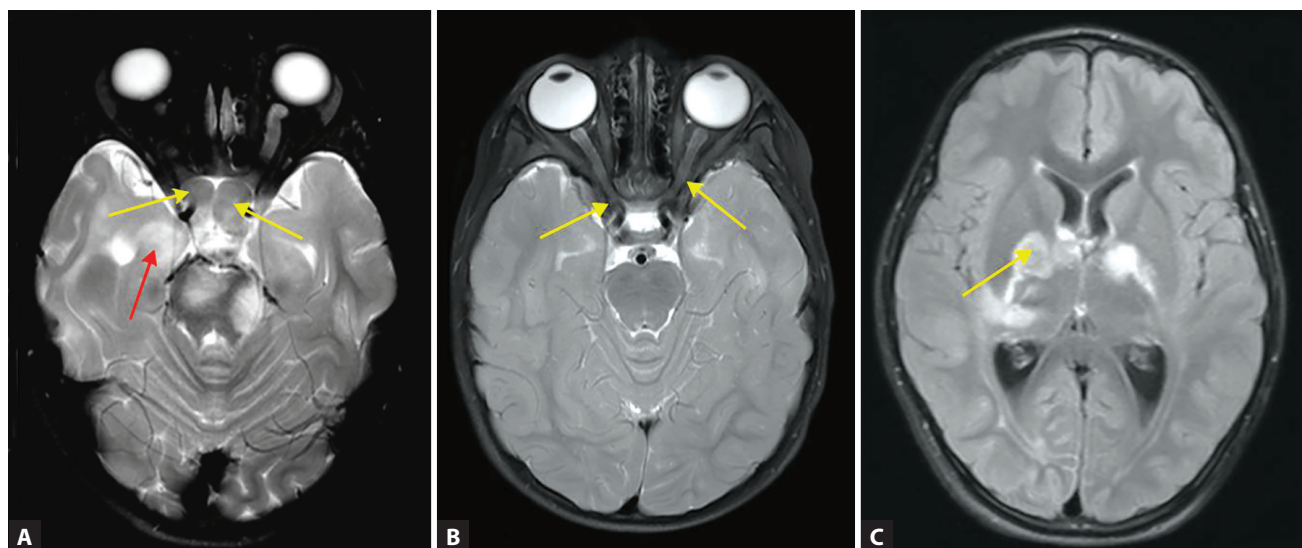
Figures 9A to C Optic glioma in a 3-year-old child seen as thickened bilateral optic nerves (yellow arrow in A) in a T2W axial image of the brain. Compare it with normal optic nerves in B, yellow arrow. A also shows high signal with mass effect (red arrow) in the medial temporal lobe and pons suggestive of an astrocytoma. Neurofibromatosis type 1 can also have focal areas of high-signal intensity (FASI); seen in C (arrow), in bilateral globus pallidus and thalamus which cause no mass effect and are asymptomatic.
Source: Dr Sniya Sudhakar, Department of Radiodiagnosis, CMC, Vellore.

Table 1 System wise complications seen in neurofibromatosis type 1 (NF1)

Clinical feature	Age of onset (years)	Frequency
Neurological		
Aqueduct stenosis	Lifelong	1.5%
Chiari I malformation	Lifelong	1.5%
Glioma—brain and spinal cord	Lifelong	2–3%
Optic pathway glioma	Birth to 7	15%
Dysembryoplastic neuroepithelial tumor	Lifelong	< 5%
Cognitive impairment IQ < 70 (learning problems)	Birth	4–8%
Epilepsy	Lifelong	6–7%
Multiple sclerosis	Adulthood	< 5%
Cerebrovascular disease	Lifelong	2.5–6%
Peripheral nervous system		
Neurofibromatous neuropathy	Adulthood	1.3%
Eye		
Congenital glaucoma	Birth	0.7%
Bone		
Scoliosis	Birth to 18	10%
Bone dysplasia with or without pseudarthrosis	Birth to 3	2%
Osteoporosis	Childhood onwards	Not known
Short stature10th–25th percentile	Birth	30%
Cardiovascular disease		
Congenital heart disease—pulmonary stenosis	Birth	2%
Respiratory system		
Restrictive lung defect	Childhood onwards	< 5%
Gastrointestinal		
Stromal tumor	Adulthood	6%
Carcinoid	Adulthood	1.5%
Other tumors		
Pheochromocytoma	> 10	2%
Breast carcinoma	Adulthood in women < 50	Five-fold increase
Rhabdomyosarcoma	Lifelong	< 5%

Surveillance involves monitoring for complications and appropriate management of the same. Dermal neurofibromas can be removed by plastic surgery, use of the CO_2 laser, or electrodessication for cosmesis. Debulking of plexiform neurofibromas is sometimes necessary both for cosmesis and to relieve pressure on the airway or spine. Optic gliomas usually do not require treatment, but progressive symptomatic lesions usually are treated with chemotherapy (vincristine and carboplatin). Radiation therapy is best avoided in young children due to vascular complications and malignancies in the radiation field. Surgical removal of tumors are indicated when they cause pressure symptoms.

It is important to educate parents about the possibility of cognitive impairment and to provide neuropsychological assessment.

NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 was considered a separate entity from the more common NF1 after a consensus conference at the National Institute of Health in 1987. With advanced neuroimaging, recent studies have suggested that the prevalence is approximately 1 in 60,000.

Etiology

Neurofibromatosis type 2 is an autosomal dominant condition with complete penetrance and variable expression characterized by multiple tumors of the nervous system and meninges as well as lesions of the eyes and skin. It results from a defect in the NF2 tumor suppressor gene situated on chromosome 22q11. Around 50–60% of patients have no family history and these represent new mutations.

Pathogenesis

The NF2 gene encodes the protein Merlin (moesin-ezrin-radixin-like protein), also called schwannomin. Merlin is localized to the cell membrane or cytoskeletal interface and influences downstream regulation of cell proliferation.

Clinical Features

Neurofibromatosis type 2 usually presents in early adulthood although milder phenotypes can present much later. Children more frequently present with visual disturbance, skin tumors or mononeuropathy whereas adults most often present with symptoms related to vestibular schwannomas.

Vestibular schwannomas **(Figs 10A and B)** are the commonest tumors to occur in NF2 and the clinical presentation is usually with hearing loss which starts unilaterally and becomes bilateral with time. The second most common tumor type encountered is meningioma which usually occurs on the cerebral convexities. Extramedullary spinal tumors like meningioma or schwannoma may also develop causing symptoms of a myelopathy.

Neurofibromatosis type 2 can also cause a neuropathy with no evidence of tumor infiltration. Children could present with a mononeuropathy affecting the facial nerve or unilateral wasted limb. In adulthood, 3–10% of patients may develop a severe polyneuropathy although up to 40% of adults show evidence of polyneuropathy on nerve conduction studies. The pathogenesis of the neuropathy is unclear but may be due to Schwann cell proliferation amongst the axons of nerves in the absence of frank tumor, the local toxic effect of tumor cells, or cellular dysfunction due to Merlin deficiency.

Up to 80% of them can have ophthalmological lesions in the form of posterior subcapsular cataract or cortical wedge opacities. Cutaneous lesions are few and include intracutaneous, plaque like lesions that are usually slightly hyperpigmented and may be covered in excess hair.

Approach to Diagnosis

Diagnostic criteria for NF2 are given in **Box 3**. Diagnosis is often delayed due to the paucity of cutaneous lesions. Depending on the clinical presentation, neuroimaging either of the brain or spinal cord will help identify the tumor. Genetic testing will detect 90% of mutations. Mosaicism can lead to segmental or unilateral involvement or milder disease.

BOX 3 Diagnostic criteria for neurofibromatosis type 2 (NF2)

Bilateral vestibular schwannomas or family history of NF2 plus
1. Unilateral VS or
2. Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities
   Additional criteria: unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities
   Or
   Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract

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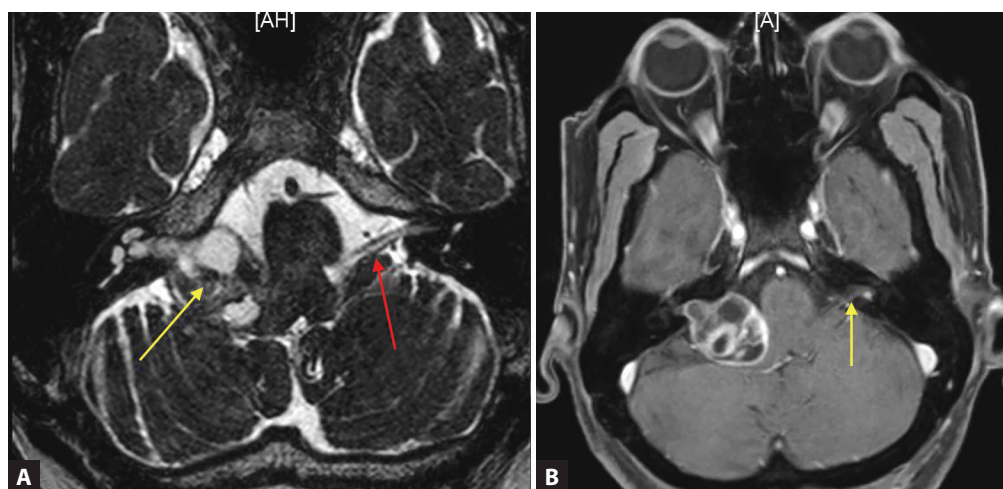
Figures 10A and B T2 drive sequence (A) and postgadolinium (B) axial images of the brain of an adult with bilateral vestibular schwannoma. The tumor on the right is large causing mass effect on the cerebellopontine angle. Compare it with the normal looking seventh eight nerve complex on the left which on the postgadolinium image (B) shows an enhancing lesion also suggestive of a schwannoma.
Source: Dr Sniya Sudhakar, Department of Radiodiagnosis, CMC, Vellore.

Management

Tumors associated with NF2 require surgical excision. Timing and extent of surgery depends on tumor size and involvement of adjacent structures. Stereotactic radiation therapy is also effective in treating tumors, but there is concern about later occurrence of malignant tumors in the radiation field. Recently bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody that inhibits the angiogenic effects of VEGF has been used in the treatment of vestibular schwannomas. The neuropathy associated with NF2 is not responsive to any form of therapy.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome (SWS) or encephalofacial angiomatosis is a sporadic disorder occurring due to early embryological malformation of the vascular system with a failure of the primitive cephalus venous plexus to regress and properly mature in the first trimester.

It is characterized by a facial capillary malformation (port-wine stain) in the ophthalmic distribution of the trigeminal nerve, with ipsilateral vascular glaucoma and vascular malformation of the eye, and vascular malformation of the brain (leptomeningeal angioma). The port-wine stain or facial angioma could be unilateral or bilateral and might extend to involve regions of the maxillary and mandibular divisions of the trigeminal nerve and in a few patients to the thorax, abdomen, and upper and lower limbs **(Fig. 11)**.

Neurological manifestations include epilepsy, focal neuro-logical deficit and psychomotor delay. Seizures which occur in 75–85% of patients are related to the leptomeningeal angioma. They are usually focal motor contralateral to the leptomeningeal angioma but can be of other types including infantile spasms. Focal neurological deficits include hemiplegia and hemianopia. Headaches and migraines are also common in SWS which may result from an increased vasogenic leakage of plasma and neuropeptides into the subarachnoid space. Ocular involvement may include eyelid hemangioma, glaucoma, conjunctival and episcleral hemangiomas, diffuse choroidal hemangiomas, and heterochromia of the irides.

MRI brain with gadolinium is the neuroimaging of choice which will show the leptomeningeal angioma and ipsilateral cerebral volume reduction **(Fig. 11)**. CT scan is superior to conventional MRI for demonstration of the characteristic calcification seen in SWS. It is seen as a double-lined gyriform pattern of calcification paralleling cerebral convolutions referred to as the railroad track sign **(Fig. 12)**.

Management of SWS involves anticonvulsants for seizures, symptomatic and prophylactic medications for headache, glaucoma treatment and laser therapy for facial angioma if they persist. Seizures are resistant to medications in about half the patients and they respond well to resective or disconnective epilepsy surgery like hemispherotomy.

OTHER NEUROCUTANEOUS DISORDER

A few other important neurocutaneous disorders are described in **Table 2**.
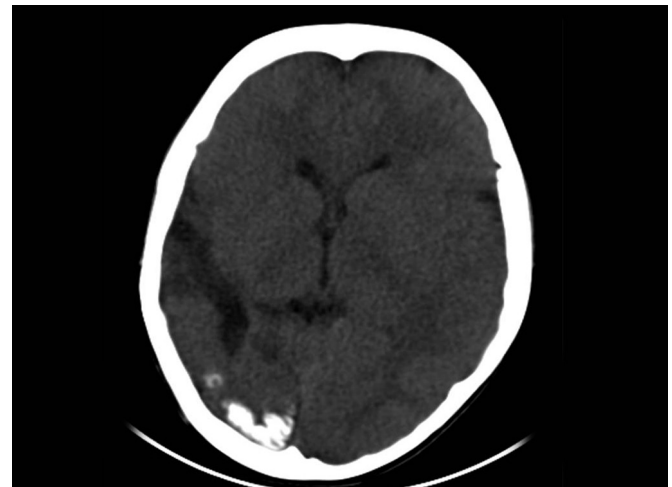
Figure 12 Plain CT brain of a child with Sturge-Weber syndrome (SWS) who underwent right posterior quadrantectomy for refractory epilepsy showing gyriform pattern of calcification over the right occipital lobe
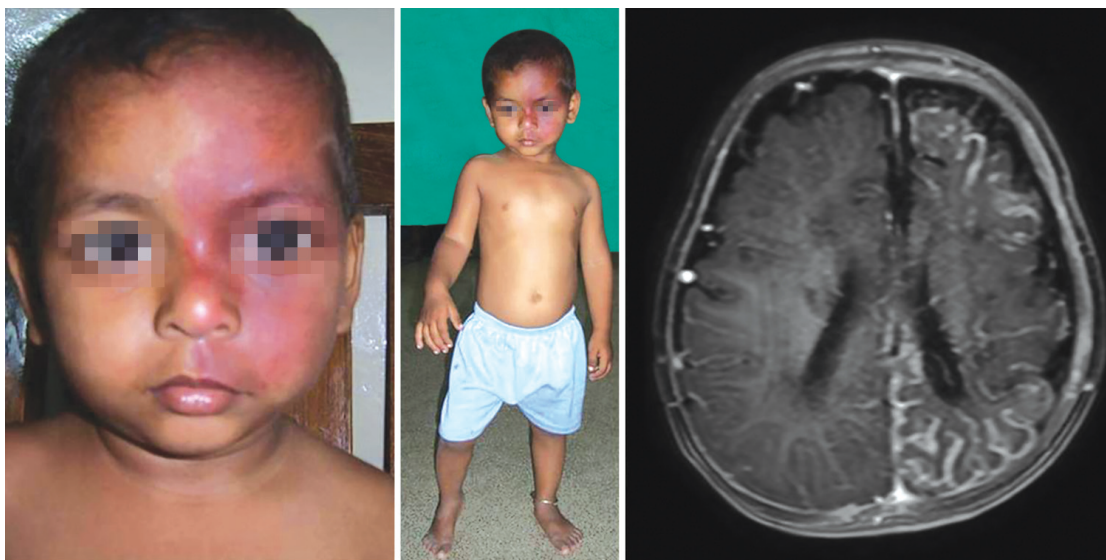
Figure 11 Child with Sturge-Weber syndrome (SWS) showing the classic port-wine stain involving the left half of the face with contralateral hemiplegia. Postgadolinium axial images of the brain show ipsilateral leptomeningeal enhancement which represent the angiomatosis and underlying left cerebral hemiatrophy

Table 2 Other neurocutaneous disorders

Syndrome	Neurologic features	Non-neurologic features	Inheritance / Gene
Schwannomatosis	Multiple schwannomas	Subcutaneous schwannomas	Autosomal dominant, INI1/SMARCB1 on chromosome 22
Epidermal nevus syndrome (Fig. 13)	Hemimegalencephaly, epilepsy, intellectual disability, focal motor deficits	Linear verrucous lesions in cranio-facial distribution, precocious puberty, renal anomalies, colobomas	Sporadic
von Hippel-Lindau disease	Retinal, cerebellar and spinal hemangioblastomas	Tumors of the pancreas, kidney, epididymis, endolymphatic sac tumors	Autosomal dominant. VHL gene on chromosome 3p25-26
Neurocutaneous melanosis	Hydrocephalus, seizures, behavioral abnormalities	Giant hairy pigmented nevi, multiple hyperpigmented cutaneous nevi	Sporadic
Hypomelanosis of Ito (Fig. 14)	Intellectual disability, seizures, ocular features such as strabismus, myopia, optic nerve hypoplasia	Linear streaks or whorls of hypopigmentation along lines of Blaschko	Sporadic
Incontinentia pigmenti (Fig. 15)	Intellectual disability, seizures, pyramidal tract dysfunction, ocular abnormalities such as retinal detachment	Hyperpigmented brown macular lesions along lines of Blaschko that evolve through 3 stages of vesiculobullous lesions, verrucous lesions and the final brown lesions	X-linked dominant, NEMO gene

Figure 13 Linear verrucous lesions along the right side of neck and face in a child with epidermal nevus syndrome. T2 fluid attenuation inversion recovery (FLAIR) axial image of the brain shows flat and thick gyri involving the entire right cerebral hemisphere suggestive of hemimegalencephaly causing left hemiparesis and refractory epilepsy
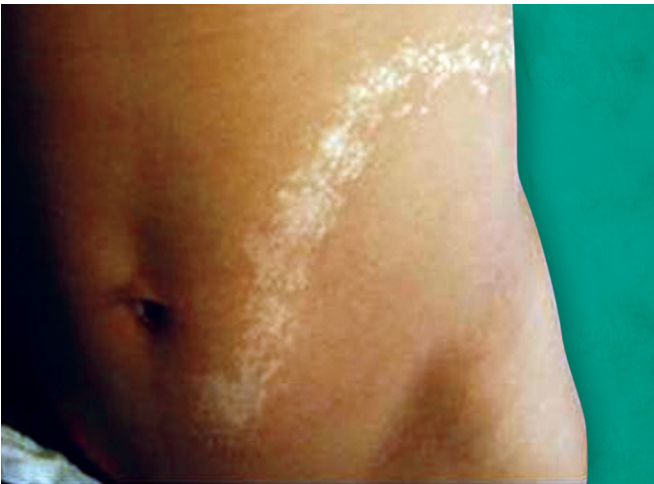
Figure 14 Linear streak of hypopigmentation along the lines of Blaschko in a child with hypomelanosis of Ito

Figure 15 Extensive hyperpigmented brown macular lesions along lines of Blaschko, the final stage of cutaneous lesion in a child with incontinentia pigmenti

IN A NUTSHELL

1. Neurocutaneous disorders are diverse group of disorders with predominant involvement of the skin and nervous system tissues.
2. Tuberous sclerosis complex (TSC) is an autosomal dominant disease, characterized by hypomelanotic macules, facial angiofibroma, facial plaque, shagreen patches, seizures and intellectual disability.
3. Neurofibromatosis type 1 is autosomal dominantly inherited with 50% representing a new mutation. Diagnosis is clinical, based on presence of café-au-lait spots (CLSs) and neuro-fibroma.
4. Neurofibromatosis type 2 is characterized by bilateral vesti-bular schwannomas.
5. Sturge-Weber syndrome is a sporadic disorder with port-wine stain and cerebral leptomeningeal angiomatosis causing seizures and focal neurological deficits.
6. Diagnosis of all neurocutaneous disorders is based on clinical criteria and once diagnosed, requires periodic follow-up for evolution of complications.
7. Genetic testing is offered when individuals reach reproductive age and to first degree relatives of the affected individual.

MORE ON THIS TOPIC

Curatolo P, Maria BL. Tuberous sclerosis. Handb Clin Neurol. 2013;111:323-31.

Elizabeth A. Phakomatoses and allied conditions. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Swaiman's Pediatric Neurology. 5th ed. USA: Elsevier; 2012. pp. 497-517.

Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): diagnosis and management. Handb Clin Neurol. 2013;115:939-55.

Laura FS. Epidermal nevus syndrome. Handb Clin Neurol. 2013;111:349-68.

Lloyd SK, Evans DG. Neurofibromatosis type 2 (NF2): diagnosis and management. Handb Clin Neurol. 2013;115:957-67.

Nabbout R, Juhász C. Sturge-Weber syndrome. Handb Clin Neurol. 2013;111:315-21.

Pinheiro A, Mathew MC, Thomas M, et al. The clinical profile of children in India with pigmentary anomalies along the lines of Blaschko and central nervous system manifestations. Pediatr Dermatol. 2007;24:11-17.

Sarnat HB, Flores-Sarnat L. Genetics of neural crest and neurocutaneous syndromes. Handb Clin Neurol. 2013;111:309-14.

Chapter 42.7
Hydrocephalus
Daljit Singh, Hukum Singh

Hydrocephalus is a clinical syndrome of raised intracranial pressure (ICP) with ventriculomegaly. It usually occurs from defective flow of cerebrospinal fluid (CSF) or rarely from excessive secretion. It should be differentiated from ventriculomegaly which is a radiological condition of large ventricle and usually asymptomatic. However both these terminologies are often interchanged. It is important to differentiate between two as hydrocephalus requires treatment where ventriculomegaly alone may not.

The first description of hydrocephalous was made by Rhazes (850-923 AD). The major evolution in the treatment of hydrocephalus happened with development of shunt procedures and later the third ventriculostomy. Dandy proposed coagulation of choroid plexus in nonobstructive hydrocephalus in 1919 and third ventriculostomy for obstructive hydrocephalus in 1922. Dandy father of neuroendoscopy, attempted endoscopic fulguration of choroid plexus. Mixter did first third ventriculocisternostomy in 1923.

The reported incidence of hydrocephalus ranges from 0.2 to 0.5/1000 births with a higher incidence has been reported in the offspring of elderly primiparous mothers.

ETIOLOGY

Hydrocephalus can be categorized as congenital and acquired **(Table 1, Figs 1 and 2)**. Causes of hydrocephalus can be classified as per the age of onset of hydrocephalus:

- *Premature infants* Posthemorrhagic hydrocephalus is seen as a sequel of intraventricular or germinal matrix hemorrhage. It leads to fibrosing arachnoiditis, meningeal fibrosis and subependymal gliosis altering the physiology of CSF flow.
- *Full-term infant* Aqueductal stenosis, Dandy-Walker malformation, tumors, Arachnoid cyst, vein of Galen malformation, Chiari malformation and intrauterine infection, and post-tubercular hydrocephalus.
- *Older children* Tumors, trauma and infection can lead to hydrocephalus due to obstruction in CSF flow along its pathway, post-tubercular hydrocephalus and brain tumors.

Functional Classification

Dandy and Blackfan described the functional division of hydrocephalus, i.e., communicating (nonobstructive) and noncommunicating (obstructive). Obstructive hydrocephalus refers to obstruction to the CSF flow within the ventricular system, such as blockage at the foramen of Monro (asymmetrical ventriculomegaly), aqueduct of Sylvius or the basal foramen of Luschka and Magendie **(Fig. 3)**. Communicating hydrocephalus on the other hand results due to obstruction outside the ventricular system, at the level of subarachnoid space or the arachnoid villi. It results due to poor absorption of CSF.

Table 1 Etiology of hydrocephalus

Congenital	Acquired
1. Aqueductal obstruction/stenosis—CSF flow is impaired when cross sectional area of aqueduct < 0.25 mm	1. Tumors and cysts obstructing the CSF pathway **(Figs 1 and 2)**
2. Arnold-Chiari malformation	2. Posterior fossa tumors
3. Chiari II malformation with myelomeningocele	3. Pineal tumors
4. Dandy-Walker syndrome	4. IIIrd ventricular tumors
5. Benign intracranial cyst	5. Choroid plexus papilloma
6. Vein of Galen aneurysm	6. Inflammation
7. Congenital CNS infection	7. Meningitis
8. Craniofacial anomalies	8. Defective absorption of CSF, e.g., TBM
9. Hydranencephaly	9. Subarachnoid hemorrhage
	10. Head injury
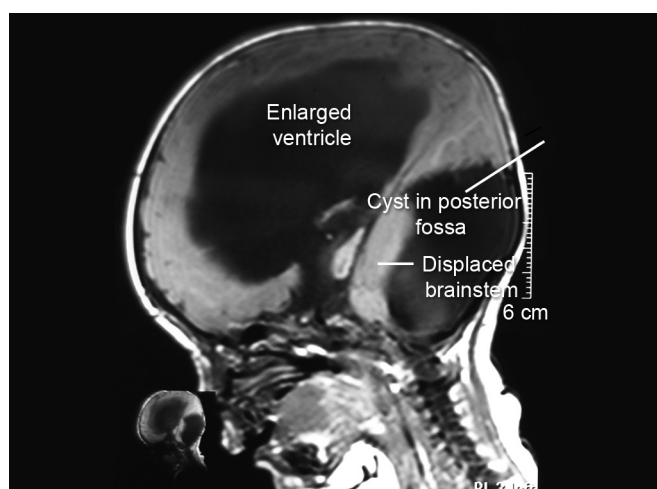
Figure 1 Cyst in posterior fossa producing obstructed hydrocephalus
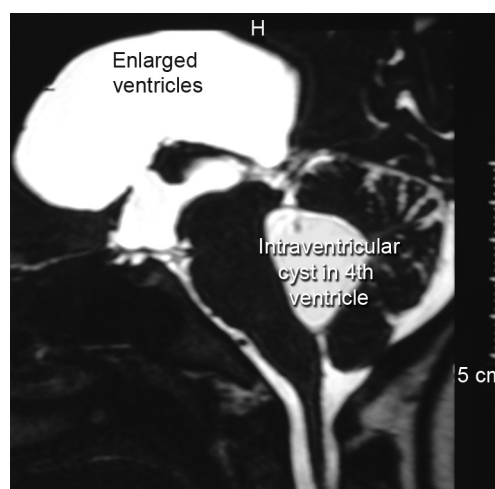
Figure 2 Intraventricular cyst in fourth ventricle with obstructed hydrocephalus
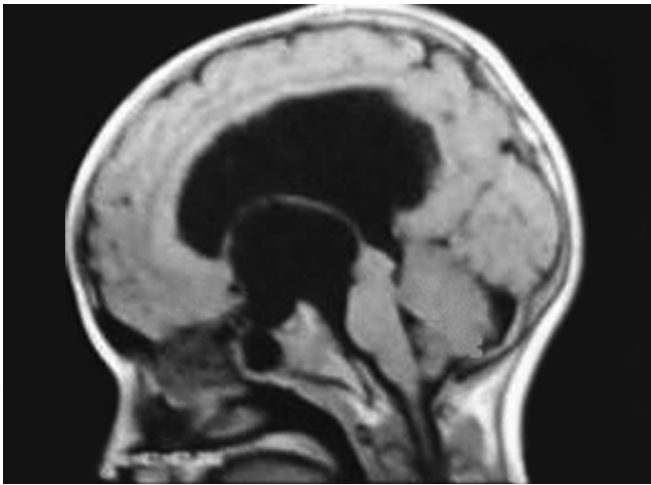
Figure 3 Aqueductal stenosis with hydrocephalus

Figure 4 Cast of ventricle depicting ventricle and flow of CSF pathway

Besides, there are certain special categories of hydrocephalus, e.g., hydrocephalus in utero, external hydrocephalus, double compartment hydrocephalus, multicystic hydrocephalus, unilateral hydrocephalus, arrested hydrocephalus, slit ventricular system and hydrocephalus *ex vacuo*.

PATHOPHYSIOLOGY

Normal CSF production is 0.35 mL/min. Capacity of lateral and third ventricle is 20 mL. Total CSF volume is 120 mL. ICP rises if production of CSF is more than absorption.

Cerebrospinal fluid is produced in the lateral ventricle by the choroid plexus. The production of CSF is an active process and is regulated by osmotic gradient as well as by enzyme carbonic anhydrase. CSF flows from lateral to third ventricle via foramen of Monro. From third ventricle, CSF flow to fourth ventricle via aqueduct of Sylvius. Length of aqueduct of Sylvius is usually 8–12 mm in length. Fourth ventricle is holds only small amount of CSF and has four opening for CSF to flow from it. A pair laterally placed foramen of Luschka, single medially placed foramen of Magendie and a central opening which leads into central canal of spinal cord. The CSF after flowing out from fourth ventricle ascends up and is absorbed by the arachnoid granulations present along the midline by superior sagittal sinus. The entire concept is known as bulk flow of CSF which was proposed by Dandy **(Fig. 4)**. CSF is also absorbed by capillaries in the subarachnoid space and 2, 7, 9 and 10th cranial nerves.

The flow of CSF inside as well as outside the ventricle is regulated by the cardiac cycle. The flow is outside the ventricle in systole and toward the ventricle in diastole. This pulsatile flow of CSF has added newer understanding in the pathogenesis of hydrocephalus **(Fig. 5)**.

CLINICAL FEATURES

The presentation of hydrocephalus is variable. It depends upon the age of patients **(Table 2)**, ability to withstand the change in the volume of CSF fluid and pulsatility of blood vessels. The clinical features are also classified as acute and chronic hydrocephalus. An increase in size of head circumference by more than 2 cm in any month is a sign of progressive hydrocephalus. In congenital hydrocephalus the infant may be normal at birth and shows subsequent enlargement of head especially at the age of nine month and at three year.
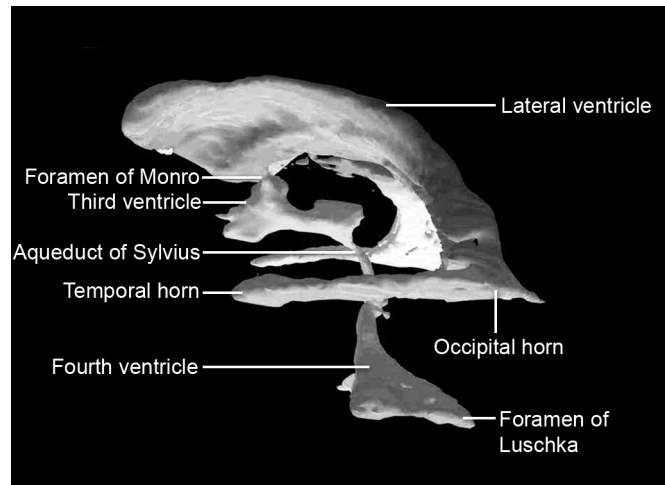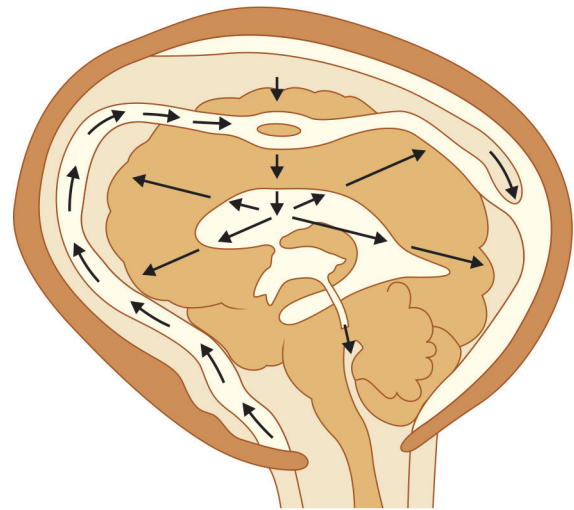
Figure 5 Pulsatile flow of CSF guided by cardiac cycle

Table 2 Clinical features of hydrocephalus according to age

Age	Symptoms	Sign
Infants	1. Poor feeding 2. Vomiting 3. Reduced activity 4. Drowsiness	1. Head enlargement 2. Dilated scalp vein 3. Tense fontanelle 4. Failure of upward gaze 5. Sunset sign 6. Increased limb tone
Children	1. Slowing of mental capacity 2. Headache 3. Vomiting 4. Vision deterioration 5. Drowsiness	1. Papilledema 2. Failure of upward gaze 3. Unsteady gait 4. Cracked pot sign 5. Large head

Acute Hydrocephalus

Acute hydrocephalus will present with headache, vomiting, nausea, respiratory difficulties (Cheyne-Stoke) and papilledema. Beside children may present with wide tense fontanels, irritability, lack of interest, and rejection of food. Neurogenic pulmonary

edema can be associated fatal condition due to refractory raised ICP. Decerebration and decortication can happen if hydrocephalus remains untreated. Altered sensorium or loss of consciousness may be terminal in such cases.

Chronic Hydrocephalus

Chronic hydrocephalus presents with enlarged head, percussion of head produces the classic cracked pot sound (McEwan sign), restricted upward gaze (Parinaud syndrome). Setting sun sign refers to weakness of upward gaze is caused when the dilated suprapineal recess compresses the quadrigeminal plate. In addition, there can be sutural diastasis, visible scalp vein and impaired mentation **(Fig. 6)**. Many a time the only presentation can be generalized seizure which is ischemic in origin. Bradycardia, hypertension, arrhythmia and asystole can be associated finding. False localizing sign, e.g., unilateral or bilateral 6th nerve palsy are not uncommon. Hydrocephalus may be associated with neural tube defects, chiari malformation, cleft palate and congenital heart disease, Dandy-Walker syndrome, primary or secondary aqueductal stenosis, neonatal infections and intracranial brain tumors.

Differential diagnosis Causes of enlarged head include familial macrocephaly, hydranencephaly, subdural effusion, rickets, and megalencephaly.

INVESTIGATIONS

The aim of investigation in hydrocephalus is to know the type of hydrocephalus, flow of CSF and extent of anatomically visible brain. These have implications in deciding type of treatment to be offered and likely functional and psychological recovery.

X-ray Skull

Plain X-ray skull is of limited value. Suture widening, erosion of posterior clinoids, silver beaten appearance and ballooning of sella can be the evidence of chronic raised ICP.

CT Head

The CT scan head provide adequate information about etiology and type of hydrocephalus. In obstructive hydrocephalus, both lateral and third ventricles are dilated. In communicating hydrocephalus there is generalized enlargement of ventricle. In addition there will be presence of CSF in subarachnoid spaces as there is defective

Figure 6 A child with hydrocephalus, with sun set sign and distended veins on scalp

absorption of CSF in such cases. Presence of periventricular lucencies and absent sulci are indicator of raised ICP and are to be considered as warning sign **(Fig. 7)**. There can be unilateral dilatation of ventricle in obstructed foramen of Monro **(Fig. 8)**, dilatation of lateral ventricle and third ventricle in aqueductal stenosis (triventriculomegaly), dilatation of lateral ventricle, third ventricle and fourth ventricle due to outlet obstruction **(Fig. 9)**. The normal bifrontal width of lateral ventricle is on average 30% of brain width at this level. When this ratio (Evans ratio) is more than 30%, it is suggestive of hydrocephalus **(Fig. 10)**.

MRI Brain

MRI scanning shows the extent of dilatation of ventricle, site and nature of block. Midsagittal scan reveals the type of aqueductal stenosis and length of obstruction. The periventricular and white matter changes are better seen in the MRI in comparison to CT scan. Cine mode MRI can show the flow of CSF via aqueduct and is helpful in establishing aqueductal stenosis and in follow-up of patency of stoma after the endoscopic third ventriculostomy (ETV).

Ultrasonography

Ultrasonography through anterior fontanelle can demonstrate ventricular enlargement in infants but provides less precise information than CT scanning. It is the procedure of choice for imaging fetal brain.

TREATMENT

The optimal treatment of hydrocephalus may vary with etiology, type of hydrocephalus and extent of emergency involved. The medical treatment shall not be prolonged for more than couple of days unless there is definite improvement with it. Many a time the symptoms of hydrocephalus are refractory to treatment. Under such situation the other causes of nonimprovement should be addressed. These include presence of vasculitis, infarction, demyelination, cerebritis, tuberculoma, ventriculitis or abscess in the brain.

Medical Treatment

Acetazolamide (Diamox), a carbonic anhydrase inhibitor reduces the CSF production. It is given as 25 mg/kg/day divided in dose, can be increased up to 100 mg/kg/day with a strict watch on electrolytes and arterial blood gas (ABG). Acetazolamide may act for noncommunicating hydrocephalus, post-tubercular hydrocephalus and as a temporary relief prior to surgical intervention. Frusemide 0.5 mg/kg and mannitol 0.25–0.5 mg/kg q 6h act as additional agents to lower intracranial temperature (ICT). These have no role to play on decreasing size of ventricles. Steroids (dexamethasone 0.25–1 g/kg/day) can be recommended for a short time in postinfective hydrocephalus just to dissolve the exudates in prepontine and subarachnoid spaces.

Surgical Interventions

Lumbar Drainage

Tapping of CSF from the spinal subarachnoid space can help in relieving ICP particularly in communicating hydrocephalus. Post-tapping headache and tonsillar herniation can be sequelae of such procedure. Lumboperitoneal shunt usage is gradually decreasing.

Ventriculoperitoneal Shunt

The most accepted surgical procedure in the treatment of hydrocephalus is ventriculoperitoneal shunt (VP shunt). The
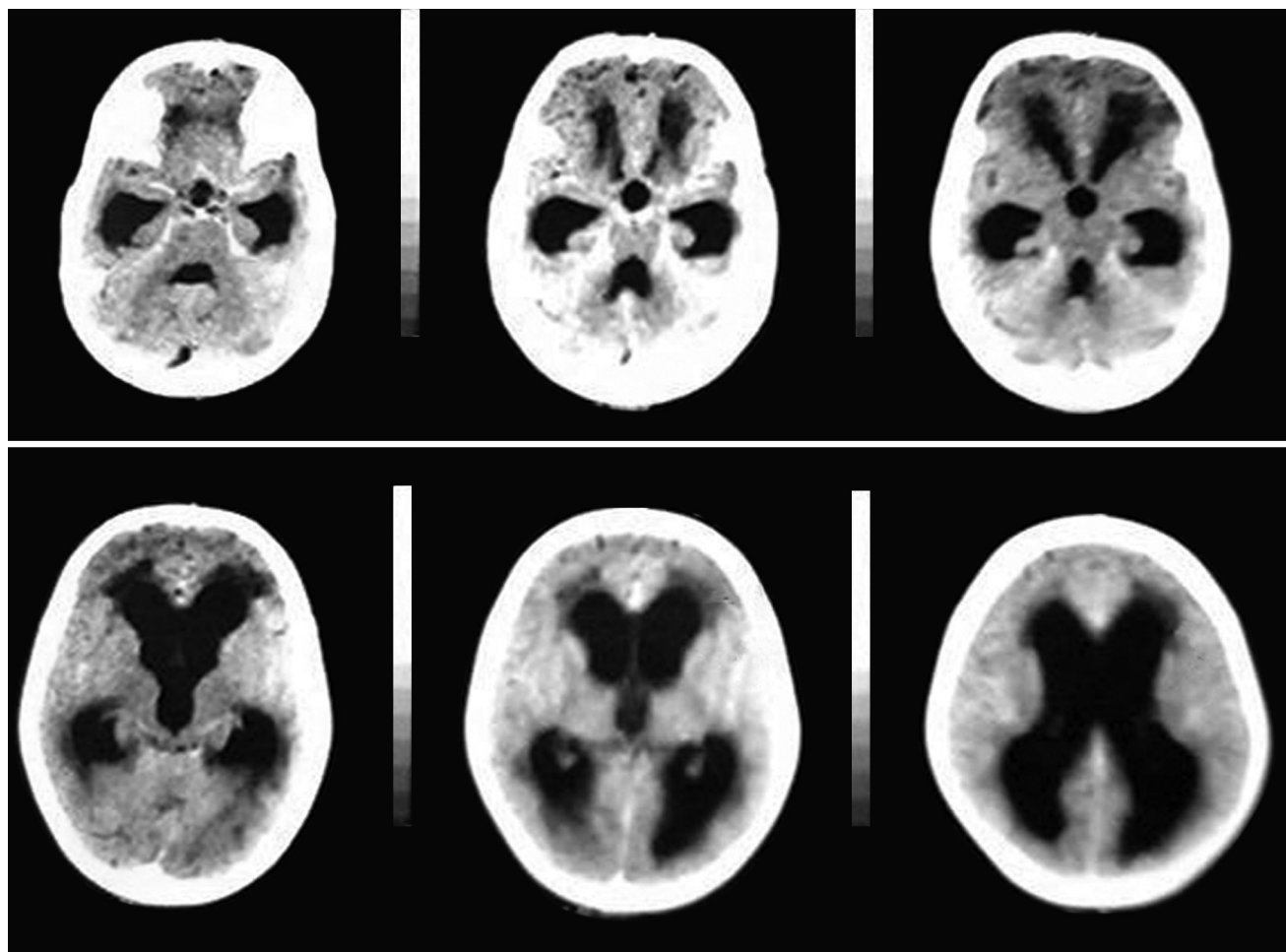
Figure 7 Presence of periventricular lucency indicating raised intracranial pressure
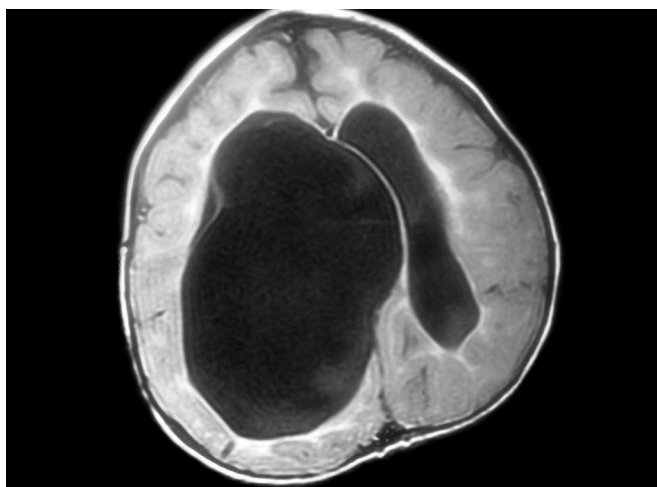
Figure 8 Asymmetrical ventricle in obstructed foramen of Monro

peritoneal end can be inserted in peritoneal cavity through open or laparoscopic techniques. The most commonly used VP shunts are Chhabra, Upadhyay and currently flow regulated shunt devices that sense the flow through a magnetic strip. The CSF from the ventricle is drained via a silicon tube into abdomen. A subcutaneous tunnel carries the shunt from the ventricle to abdomen. VP shunt is a standard surgical treatment. There are several complications that can be associated with it, e.g., infection, shunt obstruction, migration **(Fig. 11)** bleeding, ascites and subdural effusion. The success rate of VP shunt is 70–90%. The prognosis depends mainly on the extent of damage to the brain before the insertion of shunt and associated anomalies. Provided treatment precedes irreversible brain damage, results are good with most children attaining normal IQs.

Ventriculoatrial Shunt
Ventriculoatrial shunt is particularly useful in the presence of abdominal disease. VA shunt leads to glomerulonephritis and endocarditis hence has been abandoned by most neurosurgeons.

Endoscopic Third Ventriculostomy
Endoscopic third ventriculostomy is an excellent minimally invasive procedure for hydrocephalus in which internal shunting is done within ventricular system. An osteomy is made along the floor of third ventricle which drains CSF in prepontine cistern, bypassing aqueduct of Sylvius obstruction. The success rate varies from 70% to 90% depending upon the initial cause of hydrocephalus, especially in aqueductal stenosis. Rescue ETV is indicated in repeated shunt failure. Complication following ETV in a large series was found 8–10%. The fatal complications are usually
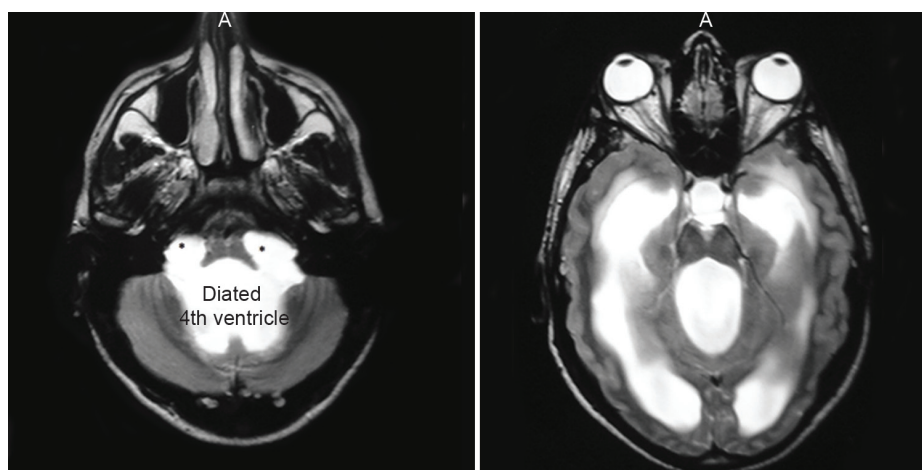
Figure 9 Fourth ventricle outlet obstruction shows dilated fourth ventricle with large foramen of Luschka

Figure 10 Ratio of (A) ventricle to (B) biparietal cortex (Evan ratio)

Figure 11 Migrated ventricular shunt per rectal

rare but can happen with rupture of basilar artery or its branch. Damage to fornix, thalamus, septal and thalamostriate vein can result during surgery and may cause neurological deficit.

MORE ON THIS TOPIC

Kandasamy J, Jenkinson MD, Mallucci CL. Contemporary management and recent advances in paediatric hydrocephalus. BMJ. 2011;343:d4191.

Wong TT, Liang ML, Chen HH, Chang FC. Hydrocephalus with brain tumors in children. Childs Nerv Syst. 2011;27:1723-34.

Stagno V, Navarrete EA, Mirone G, Esposito F. Management of hydrocephalus around the world. World Neurosurg. 2013;79(2 Suppl):S23.e17-20.

Singh D, Gupta V, Singh H, et al. Endoscopic third ventriculostomy in obstructed hydrocephalus. Neurol India. 2003;51:39-42.

Zahl SM, Egge A, Helseth E, Wester K. Benign external hydrocephalus: a review, with emphasis on management. Neurosurg Rev. 2011;34:417-32.

Zakaria R, Kandasamy J, Khan Y, et al. Raised intracranial pressure and hydrocephalus following hindbrain decompression for Chiari I malformation: a case series and review of the literature. Br J Neurosurg. 2012;26:476-81.

IN A NUTSHELL

1. Hydrocephalus is a clinical syndrome of raised intracranial pressure with ventriculomegaly.
2. Aqueductal stenosis, Chiari malformation, and Dandy-Walker syndrome are the main causes of congenital hydrocephalus.
3. Tubercular meningitis and intracranial tumors are predominant causes of acquired hydrocephalus in children.
4. Acute hydrocephalus presents with headache, vomiting, nausea, respiratory difficulties and papilledema. Chronic hydrocephalus presents with enlarged head, McEwan sign, restricted upward gaze, and setting sun sign.
5. Familial macrocephaly, hydranencephaly, subdural effusion, rickets, and megalencephaly should be considered in the differential diagnosis.
6. Neuroimaging is the mainstay of diagnosis.
7. Medical management includes acetazolamide, mannitol, and furosemide. Ventriculoperitoneal shunt is the most common surgical procedure for relief of hydrocephalus.

Chapter 42.8
Seizures and Epilepsy
Puneet Jain, Lakshminarayanan Kannan

Seizures are the most common neurological problem encountered in children and are often a frightening experience for the parents or caretakers. Epilepsy affects 0.5–1% of the population in India according to various estimates. Majority of epilepsies have onset in childhood.

Seizure is a symptom of central nervous system (CNS) dysfunction due to any cause. Seizures may occur in a myriad of conditions ranging from simple provoking factors like sleep deprivation, drug toxicity and drug withdrawal to CNS insults of any cause. Occurrence of seizures is necessary but per se is not sufficient for the diagnosis of epilepsy. Epilepsy is a condition characterized by the occurrence of recurrent unprovoked seizures.

Epilepsy is not a single disease. It is a heterogeneous group of diseases of diverse etiologies. Epilepsy is a clinical diagnosis. There is no investigation that confirms the diagnosis of epilepsy. Electroencephalogram (EEG), at best, supports the clinical diagnosis of epilepsy. A normal EEG does not rule out epilepsy and at the same time an abnormal EEG by itself is not diagnostic of epilepsy.

DEFINITIONS

An *epileptic seizure* be defined in as *'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain'* [*International League Against Epilepsy* 2005 (ILAE 2005)]. Operationally, these signs or symptoms may include sudden and transitory abnormal phenomena such as alterations of consciousness, or involuntary motor, sensory, autonomic, or psychic events perceived by the patient or an observer.

Epilepsy is defined as *a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition. The definition requires the occurrence of at least one epileptic seizure* (ILAE 2005). This is a conceptual definition. For epidemiological purposes, epilepsy is said to occur if there are at least two unprovoked seizures occurring more than 24 hours apart. This definition excludes single cluster occurring within a 24-hour period, single episode of status epilepticus, febrile seizures, neonatal seizures, and acute symptomatic (or provoked) seizures.

Acute symptomatic (or provoked) seizures occur in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute CNS insult (infection, stroke, trauma, intracerebral hemorrhage, or acute alcohol intoxication or withdrawal). Seizures occurring within 7 days of cerebrovascular disease, cerebral hypoxia, CNS infection and traumatic brain injury are classified as acute symptomatic. Similarly, seizures occurring in association with tuberculoma or brain abscess are acute symptomatic when occurring during the treatment. Seizures in a child with neurocysticercosis are acute symptomatic if occurring during the transitional or degenerative phase of the parasite (on neuroimaging). If they occur with the viable parasites (acute phase) or calcified granuloma (calcified phase), the seizures are traditionally classified as unprovoked. Seizures in association with arteriovenous malformations are acute symptomatic during the acute hemorrhage. The documented metabolic abnormality on blood sample (e.g., hypoglycemia, hypocalcemia, hyponatremia, etc.) should be within 24 hours of the seizure for the seizure to be classified as acute symptomatic seizure in association with that metabolic condition.

CLASSIFICATION

The most recent classification system was proposed in 2010 by Berg et al. Presented here is a classification of broad categories of seizures and epilepsies **(Boxes 1 and 2)**. The classification of epilepsies incorporates the ictal phenomenology, seizure type, epilepsy syndrome, underlying etiology, co-morbidities and impairments.

Epilepsy Syndrome

It is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder. These are distinctive disorders identifiable on the basis of a typical age onset, specific EEG characteristics, seizure types, and often other features which, when taken together, permit a specific diagnosis. The diagnosis in turn often has implications for treatment, management, and prognosis.

EPIDEMIOLOGY

The overall incidence of childhood epilepsy is approximately 40 cases per 100,000 children per year in the developed countries. The highest incidence rate is observed in infancy with a peak in the first week of life with subsequent decline with age. The reported prevalence rate varies within countries and tends to increase with age. In India, the reported prevalence rates are 5 to 22 per 1,000. The prevalence rates are believed to be higher in developing countries due to high incidence of adverse perinatal events, CNS infections including parasitosis and head trauma.

The overall risk of recurrence of seizure is around 40% after first seizure and 80% after the second seizure. Majority of recurrences will occur within the first 6 months (around 75%). The presence of a remote symptomatic cause, focal seizures, intellectual handicap and EEG abnormalities increase the risk of seizure recurrence. Most children do not have many seizures. Less than one-third of children with focal or convulsive seizures will have more than or equal to 10 seizures in first 10 years after diagnosis.

CLINICAL EVALUATION

The history and physical examination are the basic tools in the evaluation of a child with seizure(s). The goals of the clinical

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BOX 1 Classification of seizures

Generalized seizures

Tonic–clonic (in any combination)

Absence (typical or atypical)

Myoclonic

Clonic

Tonic

Atonic

Focal seizures

Without impairment of consciousness or awareness (old term: simple partial seizure)

With observable motor or autonomic components

Involving subjective sensory or psychic phenomena only (aura only)

With impairment of consciousness or awareness (old term: complex partial seizures)

Evolving to a bilateral, convulsive seizure (old term: secondary generalized seizure)

BOX 2	Epilepsy/electroclinical syndromes arranged by age at onset* (Berg et al 2010)

Neonatal period

  Benign familial neonatal epilepsy (BFNE)

  Early myoclonic encephalopathy (EME)

  Ohtahara syndrome

Infancy

  Epilepsy of infancy with migrating focal seizures

  West syndrome

  Myoclonic epilepsy in infancy (MEI)

  Benign infantile epilepsy

  Benign familial infantile epilepsy

  Dravet syndrome

  Myoclonic encephalopathy in nonprogressive disorders

Childhood

  Febrile seizures plus (FS+) (can start in infancy)

  Panayiotopoulos syndrome

  Epilepsy with myoclonic atonic (previously astatic) seizures

  Benign epilepsy with centrotemporal spikes (BECTS)

  Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)

  Late onset childhood occipital epilepsy (Gastaut type)

  Epilepsy with myoclonic absences

  Lennox-Gastaut syndrome

  Epileptic encephalopathy with continuous spike-and-wave
    during sleep (CSWS)

  Landau-Kleffner syndrome (LKS)

  Childhood absence epilepsy (CAE)

Adolescence – Adult

  Juvenile absence epilepsy (JAE)

  Juvenile myoclonic epilepsy (JME)

  Epilepsy with generalized tonic-clonic seizures alone

  Progressive myoclonus epilepsies (PME)

  Autosomal dominant epilepsy with auditory features (ADEAF)

  Other familial temporal lobe epilepsies

Less specific age relationship

  Familial focal epilepsy with variable foci (childhood to adult)

  Reflex epilepsies.

*Certain syndromes are often referred to as epileptic encephalopathies (P. 2101)

evaluation are confirmation of the paroxysmal event as epileptic, defining the semiology and establishing the etiology and identification of any epilepsy syndrome. Questions to be answered while evaluating a child with seizures:

- Is it a seizure or a seizure mimic (e.g. syncope, breath holding spell, etc.)?
- Is it provoked or unprovoked?
- Is the seizure focal or generalized?
- What is/are the seizure type(s)? (myoclonic, absence, atonic, etc.)
- Are there any co-morbidities? (e.g., mental retardation, cerebral palsy, etc.)

- What is the likely epilepsy syndrome?
- What is the likely etiology?

Confirmation of the Paroxysmal Event as *Epileptic*

The diagnosis of seizures or epilepsy is predominantly based on the clinical history. It often requires detailed and meticulous and patient questioning of the parents or anybody else (e.g., school teacher) who has witnessed the event. Establishing a paroxysmal clinical event as an epileptic seizure is a vital first step towards the correct diagnosis of epilepsy. Ruling out a nonepileptic paroxysmal event is important. These seizure mimickers are detailed in chapter on nonepileptic paroxysmal disorder.

The parent or caregiver may be asked to demonstrate or imitate the event. If necessary, the doctor may also demonstrate the seizure semiology for the parent or caregiver to recognize. Home videos recorded by parents using mobile phones are very useful tool in this regard. There are five important aspects to the eye witness account of any paroxysmal event. These are aura (any warning symptom?), the start (how did the event start?), the progression (how did it progress?), the associated features (what are the accompaniments?), the postictal manifestations (what happened just after the end?). This systematic account is of immense help not only in ascertaining any event as seizure or not but also in classifying seizure as focal or not.

To Classify Seizures as Focal or Generalized

The following features indicate focal origin of seizures: aura, focal involvement early in the seizure (before secondary generalization), tonic deviation (or version) of head or eyes to one side, asymmetric involvement of limbs during any part of a seizure, presence of autonomic features like flushing, change in breathing, immediate postictal focal functional impairment (Todd's paresis).

Generalized Seizures

Generalized tonic-clonic seizure Primary generalized tonic-clonic seizure *(GTCS)* may arise de novo or follow clusters of myoclonic jerks or absences (seen in idiopathic generalized epilepsies). GTCS starts with opening of eyes, tonic deviation of head and eyes (±) followed by a *tonic phase* characterized by sustained contraction of all skeletal muscles. This phase may be characterized by forced closure of the mouth, tongue biting, *epileptic cry* and cyanosis. The tonic phase ends with a *vibratory tremor* usually involving distal and facial muscles. This is followed by *clonic phase* with continuous clonic jerks of facial, trunk and limb muscles. Its duration is variable with decreasing force, amplitude and frequency of jerks with time. The *recovery phase* starts with the cessation of the clonic jerks and is characterized by unresponsiveness, bronchial secretions, urinary and rarely fecal incontinence. There is gradual recovery. Significant autonomic changes occur from the onset of GTCS with peak at the end of the tonic phase and subsequent recovery. In children, tonic phase may be longer than the clonic phase.

Generalized tonic seizures They are characterized by sustained muscular contractions (> 2 s) only without clonic components.

Generalized clonic seizures They are characterized by rhythmic clonic convulsions only. *Myoclonus*: It is a sudden brief (< 100 ms) involuntary shock-like contraction of muscle(s) or muscle groups of variable topography. They may be focal, segmental, multifocal or generalized. They may be physiological, epileptic (cortical) or non-epileptic (sub-cortical).

Epileptic spasms The term epileptic spasm is preferred to *infantile spasm* as they can occur in any age. Spasms are sudden and brief (0.2–2 s) tonic contractions of the axial and proximal limb muscles with abrupt onset and termination. They may occur in clusters or isolated. They may be flexor, extensor or mixed; symmetrical or

asymmetrical. Spasms may be subtle appearing as facial grimacing, isolated eye movements, yawning, gasping or transient focal motor activity. The spasms are accompanied by various autonomic changes. They may be followed by cry or laughter. Epileptic spasms predominantly occur on awakening or in awake state and rarely occur in sleep.

Tonic seizures It involves sudden loss of muscle tone (1–2 s) without preceding myoclonic or tonic event, involving head, jaw, trunk or limb muscles. It may manifest as only head drop to a fall. Consciousness is usually preserved.

Absence seizures Typical absences are brief seizures with abrupt onset and termination lasting for 5–20 s, usually occurring multiple times in a day. They are characterized by variable impairment of consciousness (inconspicuous, mild, moderate or severe) and classical generalized 3 Hz spike-wave-discharges on ictal EEG. They are usually precipitated by hyperventilation. Typical absence seizures may be associated with myoclonic components involving eyelids, eyebrows, corner of the mouth and rarely nostrils lasting for a brief time usually at the onset of the seizure. Automatisms (lip licking, smacking, swallowing, fumbling with clothes, etc.) and autonomic disturbances are common.

Atypical absences are usually longer with inconspicuous onset and termination. The impairment in consciousness is usually variable and subtle with significant tone abnormalities and gradual postictal recovery. They usually occur in children with severe psychomotor retardation or learning disabilities and are accompanied by other seizure types.

Drop attack is a peculiar ictal phenomenology seen predominantly in children, and occurs with epileptic spasms, tonic, atonic, myoclonic seizures and atypical absences. Drop attacks can be very dramatic and injurious at times.

Focal Seizures

Without impairment of consciousness or awareness (simple partial seizure) This a type of focal seizures where the patient retains awareness and responsiveness to the environmental cues appropriately. There may or may not be any motor automatisms.

With observable motor or autonomic components Autonomic features may be in the form of pallor, sweating, flushing, increased or rarely decreased heart rate or change in respiration. Motor component may include focal tonic or dystonic posture or clonic jerking.

Establishing the Etiology and Identification of Epilepsy Syndrome

Etiology and syndromic diagnosis of epilepsies are vital for management and prognosis. Important medical history includes:
- Age of onset of seizures
- Seizure types, evolution
- Previous history of febrile seizures (simple/complex)
- Associated features
- Developmental trajectory: normal, stagnation, regression
- Pointers towards inborn error of metabolism **(Table 1)**
- Comorbidities
- Detailed birth and peri-/antenatal history
- Previous history of trauma or CNS infection
- Family history

Clinical examination should include anthropometry, dysmorphism, neurocutaneous features and detailed neurological and systemic assessment. It is also important to screen for various comorbidities like tone abnormalities, contractures, vision or hearing deficits, dental hygiene, difficulty in feeding

Table 1 Affected genes in epilepsy

Epilepsy	Genes affected
Benign familial neonatal seizures	KCNQ2, KCNQ3
Benign familial neonatal-infantile seizures	SCN2A
Genetic epilepsy with febrile seizures plus (GEFS)	SCN1A, SCN1B, GABRG2
Early-onset absence epilepsy	SLC2A1
Juvenile myoclonic epilepsy	EFHC1, GABRA1
Autosomal dominant nocturnal frontal lobe epilepsy	CHRNA4, CHRNB2, CHRNA2
Autosomal dominant partial epilepsy with auditory features	LGI1
X-linked infantile spasms/Rett syndrome	CDKL5/STK9
Ohtahara syndrome	ARX, STXBP1
Epilepsy and mental retardation limited to Females	PCDH19
Dravet syndrome	SCN1A

or malnutrition, sleep disorders and behavioral disorders, and adverse effects of the antiepileptic drugs (AEDs).

GENETICS OF EPILEPSY

In recent years, there are newer genetic mutations identified in the causation of epilepsy. This has many implications not only for diagnosis but also for the treatment modalities used and the prognosis. For example, it is well known now that lamotrigine causes worsening of seizures in Dravet syndrome. Thus, whenever SCN1A spectrum is suspected lamotrigine should be avoided. There are panel of gene tests commercially available for epileptic encephalopathy and other epilepsy syndromes. **Table 1** lists some of the examples of epilepsy syndromes and the respective genes affected.

ROLE OF EEG

When used judiciously, EEG is the single most useful tool in managing patients with epilepsy optimally. EEG can only support a clinical diagnosis of epilepsy when it is abnormal but cannot exclude epilepsy when it is normal. EEGs may be normal in some patients with epilepsy (e.g., early EEGs in Dravet's syndrome, insular seizures, frontal lobe epilepsy and simple partial seizures including epilepsia partialis continua).

On the other hand EEG abnormality per se does not mean that the patient has epilepsy. A patient with *genetic trait* has an epileptiform EEG but does not necessarily always manifest the disease. EEG abnormality may be seen in first degree relatives with epilepsy. As it is true for many clinical situations, a patient needs to be treated as a whole and not the EEG. There are few exceptions, wherein one needs to aggressively treat EEG abnormalities such as hypsarrhythmia, epileptic encephalopathy, electrical status epilepticus in slow wave sleep (ESES) even if the patient has only few clinical seizures. Indications of EEG are listed in **Box 3**.

Role of prolonged video EEG monitoring Long-term video-EEG monitoring is very essential part of epilepsy presurgical evaluation. Clinical situations where video EEG proves useful are listed below: To characterize events (e.g., nocturnal frontal lobe epilepsy versus parasomnia).
- Gold standard for diagnosing psychogenic nonepileptic events
- To characterize semiology and to classify epilepsy syndrome
- Presurgical evaluation (to define ictal onset zone).

ROLE OF NEUROIMAGING IN EPILEPSY

In cases of new-onset focal seizures, imaging abnormality can be expected in up to 50% of cases. But of these, only in 15–20% of cases imaging provides useful information on etiology of the underlying condition. Imaging results potentially altered immediate medical or surgical management in a minority of these patients (2–4%).

Thus, neuroimaging should be utilized judiciously for epilepsy patients in resource limited settings like ours. Ordering neuroimaging when it is not indicated [as in cases of childhood absence epilepsy (CAE)] is clear wastage of resources and time. There are four broad goals for imaging a patient with epilepsy: (1) to identify patients in whom alteration in medical or surgical management would ensue with imaging results, (2) to localize a lesion (site of seizure origin), (3) to establish etiology of epilepsy, (4) to determine prognosis. Imaging is not indicated in CAE, idiopathic generalized epilepsy, benign childhood epilepsies and when genetic syndromes (Down syndrome, Angelman syndrome, etc.) are suspected. Indications for neuroimaging are listed in **Box 4**. MRI is the imaging modality of choice whenever neuroimaging is indicated in epilepsy. CT scan may be used an initial investigation in resource-limited settings, where intracranial granulomas (neurocysticercosis) are common causes of seizures.

FIRST UNPROVOKED SEIZURE

An unprovoked seizure is *a seizure or a cluster of seizures occurring within 24 hours in a child older than 1 month of age, occurring in the absence of precipitating factors*. Thus, a seizure flurry occurring within 24 hours with return to baseline between seizures is typically considered to represent as a first seizure. It is also important to note that the first unprovoked seizure will be status epilepticus in 10–20% cases. The incidence of unprovoked seizures ranges from 50 to 70 per 100,000 with higher prevalence in children younger than 1 year of age.

The investigations must be individualized. If the seizure appears focal, or secondarily generalized, neuroimaging (MRI or CT) is appropriate. If the patient has absence seizures, or the history is very suggestive of rolandic epilepsy, EEG is the investigation of choice.

EPILEPTIC ENCEPHALOPATHIES

The term *epileptic encephalopathy* refers to a group of disorders in which the unremitting epileptic activity contributes to progressive neurological dysfunction. This cannot be explained by the

underlying etiology alone. The underlying etiology is diverse. Their clinical and electroencephalographic (EEG) features reflect the specific age-related epileptogenic reaction of the immature brain. The various syndromes of epileptic encephalopathy are tabulated in **Box 5**.

Early Infantile Epileptic Encephalopathies

This group of disorders comprises of Ohtahara syndrome or early infantile epileptic encephalopathy (EIEE) and early myoclonic encephalopathy (EME).

Ohtahara syndrome is a catastrophic epilepsy with onset ranging from intrauterine period to 3 months of age. The defining seizure types are frequent *tonic spasms* that occur in both sleep and wakeful states. Besides these, partial and rarely myoclonic seizures may be observed. The inter-ictal EEG shows burst suppression pattern with no sleep-wake differentiation.

The underlying causes are heterogeneous. The majority of cases are attributable to static structural brain lesions such as focal cortical dysplasia, hemimegalencephaly, and Aicardi syndrome. Few genetic mutations have been described but these are not specific for Ohtahara syndrome.

Early myoclonic encephalopathy presents within first 3 months of age and mostly within the neonatal period. Fragmentary erratic myoclonia, partial seizures and less frequently tonic spasms are seen. The interictal EEG shows burst suppression pattern more prominent during the sleep. The etiologies include inborn errors of metabolism (such as nonketotic hyperglycinemia, organic acidemias, Menkes disease, Zellweger syndrome), genetic factors and rarely structural abnormalities.

The seizures in these syndromes are often drug-refractory. The ketogenic diet has been tried with limited success. Neurosurgery is sometimes favorable in selected cases of cerebral malformations. The prognosis is uniformly poor with survivors left with severe psychomotor retardation. There may be *age-dependent evolution* in Ohtahara syndrome to West syndrome and then subsequently to Lennox-Gastaut syndrome (LGS).

West Syndrome

West syndrome was first described by W.J. West in 1841 and is characterized by epileptic spasms or *salaam attacks*, hypsarrhythmia/variants on EEG and developmental arrest or regression. West syndrome is one of the age-related epileptic encephalopathy with a typical onset is between 3 months and 12 months of age. The epileptic spasms are clusters of sudden, brief diffuse or fragmented, tonic contractions of axial and limb muscles. Spasms are longer than myoclonic jerks and shorter then tonic seizures in duration. The spasm clusters may be accompanied by cry, laughter or autonomic changes. It may be flexor (most common), extensor, mixed or subtle. They usually occur on arousal and in alert states.

The etiology is diverse. West syndrome has been classically classified into symptomatic (identifiable neurological insult), cryptogenic (probably symptomatic but with no known etiology)

and idiopathic (normal premorbid development and unknown etiology) forms. The classification as per new ILAE classification is shown in **Box 6**. Thus, a thorough clinical evaluation followed by appropriate neuroimaging and genetic and metabolic work-up is warranted in a child with West syndrome.

Epileptic spasms can occur with or without hypsarrhythmia in EEG. When infantile spasms are associated with hypsarrhythmia and development arrest or regression, this fulfills the criteria for West syndrome. Hypsarrhythmia is a specific EEG pattern with chaotic background activity and very high amplitude sharp and spike-slow waves over bilateral posterior quadrants. Hypsarrhythmia is an essential part of the diagnosis of West syndrome.

Infantile spasms require different approach to treatment compared to other seizures occurring in this age group. Hormonal therapy [adrenocorticotrophic hormone (ACTH) or oral prednisolone] is the treatment of choice for short-term treatment of epileptic spasms. Vigabatrin is a second-line drug except in children with tuberous sclerosis complex where it is the preferred drug. Recent literature also supports an early trial of oral pyridoxine. Drugs like phenytoin, carbamazepine may cause worsening of spasms and phenobarbitone is mostly not effective. The ketogenic diet has also shown to be beneficial. Neurosurgery may be warranted in refractory selected cases.

The prognosis is guarded and is governed by the underlying etiology and the timeliness of specific treatment. A common mistake that delays initiation of specific therapy is to treat epileptic spasms with phenobarbitone, sodium valproate and other AEDs that are not very effective in this context. The earlier the condition is recognized and the specific therapy started the better is the neurodevelopmental outcome. The affected children are left with variable psychomotor retardation, epilepsy or behavioral disorders.

Dravet Syndrome

It was first described by Charlotte Dravet in 1978 as severe myoclonic epilepsy of infancy (SMEI). The onset is usually between 5 months and 8 months of age with frequent, prolonged febrile unilateral clonic convulsions with alternating pattern in a previously normal child. Non-febrile prolonged GTCSs may also be present. This stage is followed by emergence of multiple seizure types (myoclonic, atypical absences and complex focal seizures) which frequently progress to status epilepticus and associated severe neurological deterioration. The initial development is normal in infancy and the development arrest or regression starts in 2–4 years of age. The relentless progression stops at around 10–12 years of age with decrease in seizure frequency and persisting neurologic sequelae.

Repeated EEGs are normal in the early phase, but shows severe abnormality later in the course of the illness. Mutations in the

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BOX 6 Classification of West syndrome

Structural/Metabolic
- Pre-, peri- and post-natal cerebral ischemia
- Cerebral malformations
- Neuro-infections sequelae
- *Neurocutaneous syndromes:* Tuberous sclerosis, incontinentia pigmenti
- Hypothalamic hamartoma
- Inborn errors of metabolism: Biotinidase deficiency and other organic acidurias, phenylketonuria, mitochondrial disorders, Menkes disease, nonketotic hyperglycinemia, pyridoxine deficiency

Genetic
- Genetic, e.g., *CDKL-5*, *MeCP 2*, *ARX*, *STXBP-1*, *SPTAN1*, *PLC-β1*
- Chromosomal disorders, e.g., Down syndrome, 1p36 deletion, Pallister-Killian syndrome
- **Unknown**

SCN1A gene encoding the alpha-1 subunit of the sodium channel are detectable in 70–80% of patients with Dravet syndrome.

Seizures are usually refractory. Drugs like carbamazepine, phenytoin and lamotrigine worsen seizures. Sodium valproate, clobazam, and topiramate are the effective AEDs in this syndrome. Stiripentol in conjunction with clobazam or valproate has recently been licensed for use in Dravet syndrome. It is said to control prolonged seizures and status epilepticus better with few patients attaining seizure freedom. Stiripentol is not available in India, but can be procured from other countries (expensive). Early initiation of ketogenic diet has been advocated.

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a severe form of epileptic encephalopathy with onset between 1 year and 8 years of age. It is characterized by *intractable* seizures of different semiologies including tonic, atypical absence, atonic and myoclonic seizures. Two-thirds of patients may have nonconvulsive status epilepticus. The cognitive deterioration or stagnation is common and fluctuates with the seizure frequency. The pathognomonic interictal EEG findings are slow-spike-and-wave discharges (1.5–2.5 Hz) and paroxysmal fast activity.

The etiology of LGS is heterogeneous and similar to epileptic spasms. Valproate and clobazam are the preferred drugs. Levetiracetam, lamotrigine, topiramate, zonisamide and rufinamide are the second line drugs. Steroids and intravenous immunoglobulins may be indicated during periods of increased seizure frequency or status epilepticus. Phenytoin, carbamazepine and intravenous benzodiazepines worsen seizures and may cause tonic status epilepticus in this context. The ketogenic diet is a useful alternative and may be used early in the management. The prognosis is guarded with more than 80% children having persistent epilepsy and severe neurocognitive sequelae.

Epileptic Encephalopathy with CSWS Including LKS

Landau-Kleffner Syndrome

The peak onset is between 5 years and 7 years of age with verbal auditory agnosia in a previously normal child. The language function continues to deteriorate and the course can be gradually progressive or fluctuating. Some children may become mute. Mild behavioral abnormalities are common. Seizures occur in majority (75%) of the children and are infrequent and usually nocturnal. Semiologies may include generalized tonic-clonic, focal motor, atypical absences, head drops and subtle seizures. The EEG is characterized by mainly posterior temporal epileptiform discharges which are markedly activated by sleep.

The main aim of the treatment is to reduce or eliminate the epileptiform discharges. Valproate, benzodiazepines and levetiracetam are the most effective drugs. Poor responders may be treated with ACTH or prednisolone. The role of intravenous immunoglobulins and ketogenic diet is unclear. For medically refractory cases, multiple subpial transection has been used with some success. The seizures and epileptiform abnormalities remit by the age of 15 years. Majority of children are left with permanent language dysfunction. The earlier the onset of LKS, the worse the prognosis with regard to the language function.

Epileptic Encephalopathy with Continuous Spike-and-wave During Sleep

The onset of this epileptic encephalopathy is between 2 months and 12 years of age. The preceding neurodevelopment is normal in 50% children. Seizures are the presenting symptom in 80% children and neuropsychological deterioration in the

rest. The children present with infrequent, nocturnal seizures (simple or complex focal, generalized tonic-clonic or myoclonic seizures). The interictal EEG during wakefulness shows focal or multifocal epileptiform discharges with marked accentuation during sleep.

After 1–2 years, there is increase in seizure frequency with emergence of new seizure types (absence or atonic seizures, negative myoclonus). This is associated with the appearance or deterioration of neurocognitive status. The interictal EEG during wakefulness shows more pronounced abnormalities. During non-rapid eye movement (NREM) sleep, EEG shows continuous or nearly continuous spike-wave discharges (CSWS). This stage is followed by clinico-electroencephalographic remission, usually 2–7 years after the onset. Majority of the children, however, are left with residual moderate to severe neurocognitive deficits.

Early initiation of steroids or ACTH is usually recommended. Intravenous immunoglobulins also have shown promising results. The AEDs, used for LKS, are usually effective. Clobazam once daily dose at night, sometimes in high doses (20–30 mg/day), is said to be effective in anecdotal reports. Limited response has been demonstrated with ketogenic diet.

GENETIC (IDIOPATHIC) GENERALIZED EPILEPSY

Idiopathic epilepsy is a concept that encompasses an otherwise structurally normal brain with epilepsy as the only neurological problem. Genetically determined lowered threshold for generalized seizures is the pathophysiologic basis for this condition. One third of epilepsies in childhood are actually genetic generalized epilepsies (GGE). GGE phenotype is an age-related electroclinical syndrome. GGE patients present with typical absences or GTCS. On detailed historical evaluation the presence of early morning myoclonus in some patients may become apparent. Many patients present with early morning GTCS in the context of sleep deprivation or provoked arousal. Patients with GGE are typically developing children with unremarkable neurologic examination. Neuroimaging is usually normal. EEG background activity is normal and the pathognomonic feature in EEG is the presence of paroxysmal, 3–4 Hz or faster, generalized spike and wave or polyspike-slow wave discharges (regular or irregular depending on the syndrome).

The following syndromes are included under the rubric of GGE:
1. Benign myoclonic epilepsy in infancy
2. Generalized epilepsy with febrile seizures plus (GEFS+)
3. Epilepsy with myoclonic astatic seizures
4. Childhood absence epilepsy
5. Juvenile absence epilepsy (JAE)
6. Juvenile myoclonic epilepsy (JME)
7. Genetic generalized epilepsy with GTCSs only

Childhood Absence Epilepsy

This is an age-related epilepsy syndrome that typically manifests in middle childhood (4–10 years of age). The usual presentation is one of multiple daily *blank spells* in a typically developing child. These episodes are usually noticed by others (parents, siblings, peers and teachers) but the patient himself is not aware. Typical absence seizures manifest as sudden ceasing of activity for few seconds (usually 5–15 s) with associated staring and other automatisms (see typical absence seizure) and prompt resumption of the activity. In untreated or inappropriately or inadequately treated patients with CAE, typical absences can readily be demonstrated by having the child blow a pinwheel (hyperventilation) for 3 min in the outpatient department. This should be attempted in every patient where typical absences are suspected.

The classical EEG abnormality is the generalized 3 Hz spike-wave pattern. Sodium valproate and ethosuximide are the drugs of choice. Most patients are responsive to monotherapy in moderate doses and remain seizure free and outgrow the seizures before 12 years of age.

Juvenile absence epilepsy presents later (7–17 years) with less frequent typical absence seizures. Majority of patients also have GTC seizures in addition to typical absence seizures, sometimes GTCSs precede the absence seizure in onset. The risk of GTCS years after complete remission of absences is known.

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy presents in adolescence (12–18 years) with GTCS predominantly in the early morning hours, just upon awakening. Usually a cluster of myoclonias herald a GTCS. All patients with JME have myoclonic jerks, 85% have GTCS and 30% have typical absence seizures. EEG shows fast 4–6 Hz irregular generalized polyspike and spike-wave complexes with 30% of patients showing photosensitivity. Seizures are easily controlled on moderate doses sodium valproate monotherapy. Levetiracetam, lamotrigine and topiramate are effective alternatives. Carbamazepine and phenytoin should be should be avoided as they worsen seizures. There is high (80%) recurrence rate of seizures after stopping AED even after many years of seizure control. Most of the patients need lifelong AED treatment.

BENIGN CHILDHOOD FOCAL EPILEPSIES

Benign childhood focal epilepsies are a group of disorders characterized by focal-onset seizures with no underlying structural brain abnormality and presumed functional mechanism for the epilepsy and EEG abnormalities. Their common features include seizures closely related to sleep, no associated neurologic signs, no or mild cognitive impairment, good response to anticonvulsant drugs, spontaneous resolution after few years, normal EEG background with EEG abnormalities greatly enhanced during sleep.

The ILAE task force recognizes three syndromes of benign childhood focal epilepsies:
1. Benign childhood epilepsy with centrotemporal spikes (BCECTS)
2. Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
3. Late-onset benign childhood occipital epilepsy (Gastaut type).

Benign Childhood Epilepsy with Centrotemporal Spikes

It is also known as Rolandic epilepsy. It is the most common age-related focal epilepsy in childhood with peak frequency of onset between 7 years and 10 years of age. It is characterized by infrequent (25% children have only one seizure) and brief seizures. Majority of the seizures are focal with generalization seen in some children. More than half of the children have seizures during sleep. The cardinal features of rolandic seizures include: *Hemifacial sensorimotor seizures:* tonic face deviation, clonic jerks of cheek or eyelids, numbness; *Oropharyngeal manifestations*: guttural sounds, gargling, hypersalivation; and *Speech arrest*. Rarely, focal motor status epilepticus may occur. There may be associated behavioral or cognitive deficits.

Electroencephalogram shows classical centrotemporal spikes, most pronounced during sleep. Neuroimaging is normal and is *not required* for the classical cases. The prognosis is excellent with remission within few years. However, atypical evolutions are known (< 1%).

Many patients with typical rolandic epilepsy do not need AED treatment, as this is an age-related condition with very infrequent seizures that almost all patients outgrow. There is a subgroup of patients with frequent or prolonged seizures who need treatment.

Sodium valproate, levetiracetam, clobazam are the preferred drugs and carbamazepine and oxcarbazepine may cause worsening of the condition.

Early Onset Benign Childhood Occipital Epilepsy (Panayiotopoulos Type)

Its peak frequency of onset is between 3 years and 6 years of age (range: 1–14 years). It is characterized by infrequent and usually prolonged seizures. Two-thirds of the children have seizures during sleep. The seizures usually begin with variable combination of nausea, retching and vomiting. Other autonomic manifestations like pallor, flushing, cyanosis, coughing or incontinence may be present. These symptoms may proceed to deviation of eyes, unilateral clonic jerks, visual symptoms and loss of consciousness. Status epilepticus and sudden cardiorespiratory arrest are known to occur. EEG shows stereotypic occipital or multifocal spike-wave discharges which are markedly activated by sleep and eye-closed state.

Carbamazepine and valproate are the commonly used drugs. Rarely, aggravation is known to occur with carbamazepine. The prognosis is excellent with majority of children achieving complete seizure remission within few years. Atypical evolutions are extremely rare.

Late Onset Benign Childhood Occipital Epilepsy (Gastaut Type)

The mean age of onset in late onset benign childhood occipital epilepsy is around 8 years (range: 3–15 years). Around 20% patients may have a family history of migraine. Majority of seizures are diurnal. They are frequent but usually brief. The seizures start with visual symptoms, including elementary or formed visual hallucinations, transient amaurosis or visual illusions. They may be followed by hemisensory, motor signs, or unresponsiveness. One-third of patients can have severe postictal, headache, sometimes with nausea or vomiting, closely mimicking migraine. EEG shows occipital paroxysms which are enhanced by sleep and eye-closed state. Children show dramatically good response to carbamazepine. Prognosis is usually good with more than half of the patients achieving remission within 2–4 years of onset.

Other Focal Epilepsies

The most common causes of childhood symptomatic focal epilepsy in our country are perinatal insult, neuroinfection sequelae and calcified granulomas. Mesial temporal lobe epilepsy (MTLE) is another common problem.

Mesial Temporal Lobe Epilepsy

Mesial temporal lobe epilepsy is a specific focal epilepsy syndrome that is commonly refractory to drug treatment. MTLE usually manifests in adolescence with habitual seizures but may present in late childhood. History of complex febrile seizures, febrile status epilepticus or encephalitis like illness in early childhood may be present in 50% of patients. The typical seizures in this syndrome is very stereotypic with visceral aura (epigastric raising sensation) and hypomotor seizures with motionless staring and behavior arrest, oral automatisms (chewing and other repeated lip movements), ipsilateral hand automatisms (fumbling, cloth picking, may appear semi purposeful) with or without head version to contralateral side or dystonic posturing of arms later in the seizures. The seizures very rarely generalize (secondary generalization). Hippocampal sclerosis is the underlying cause in most of the patients but there may be other lesions in mesial temporal lobe such as tumors [ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET)], cortical dysplasia or developmental venous anomaly. Carbamazepine or oxcarbazepine are the usual first line drugs. Some patients are refractory from the beginning but most of the

patients remit for a variable period only to recur later and become drug refractory. Lamotrigine, clobazam, topiramate, lacosamide are effective in some patients who failed on first line drugs. Epilepsy surgery is considered when there is drug resistance. MTLE is one of the most common causes of drug refractory epilepsy in adolescents and young adults. Selective amygdalohippocampectomy with or without anterior temporal lobectomy is a curative surgery with a remission rate of nearly 80%.

IN A NUTSHELL

1. An epileptic seizure can be defined in as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
2. Acute symptomatic (or provoked) seizures occur in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute CNS insult (infection, stroke, trauma, intracerebral hemorrhage, or acute alcohol intoxication or withdrawal).
3. Etiology and syndromic diagnosis of epilepsies is vital for management and prognosis.
4. Seizures are broadly classified as generalized or focal.
5. Electroencephalogram can only support a clinical diagnosis of epilepsy when it is abnormal but cannot exclude epilepsy when it is normal.
6. In cases of new-onset focal seizures, imaging abnormality can be expected in up to 50% of cases.
7. West syndrome is characterized by epileptic spasms or salaam attacks, hypsarrhythmia/variants on EEG and developmental arrest or regression.
8. Lennox-Gastaut syndrome (LGS) is a severe form of epileptic encephalopathy with onset between 1 years and 8 years of age. It is characterized by intractable seizures of different semiologies including tonic, atypical absence, atonic and myoclonic seizures.
9. Benign childhood focal epilepsies are a group of disorders characterized by focal-onset seizures with no underlying structural brain abnormality and presumed functional mechanism for the epilepsy and EEG abnormalities.
10. The most common causes of childhood symptomatic focal epilepsy in our country are perinatal insult, neuroinfection sequelae and calcified granulomas.

MORE ON THIS TOPIC

Aneja S, Jain P. Refractory epilepsy in children. Indian J Pediatr. 2014 (In press)
Berg AT1, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676-85.
Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014;55:475-82.
Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46:470-2.
Foldvary-Schaefer N, Unnwongse K. Localizing and lateralizing features of auras and seizures. Epilepsy Behav. 2011;20:160-6.
Gaillard WD, Chiron C, Cross JH, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50:2147-53.
Guerrini R, Pellacani S. Benign childhood focal epilepsies. Epilepsia. 2012;53 Suppl 4:9-18.
Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2003;60:166-75.
Jain P, Sharma S, Tripathi M. Diagnosis and management of epileptic encephalopathies in children. Epilepsy Res Treat. 2013;2013:501981.
Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011;52 Suppl 7:2-26.

Chapter 42.9
Treatment of Seizures and Epilepsy
Gopinath Musuwadi Subramanian

The management of epilepsy is multidimensional and encompasses several issues centered on the child and the family than a mere act of prescribing medications. The management principles across different types of epilepsies may overlap and share similarities but they should be individualized to a particular child taking into account all relevant factors other than epilepsy.

Bearing the label of epilepsy aside, the immediate and long-term effects of such epilepsy can be far reaching to the child and the family. A single seizure can have disastrous consequences on a child's life at home, school and society. Such events can cause major impact on the family's social, life style and financial aspects and a compulsion to adapt to the new reality. A single event can raise ongoing uncertainty all the way for weeks, months, or years until the diagnosis is entertained or confirmed. Recurrent seizures on the other hand, affect not only the personal and school life of a child or adolescent but also affect the entire family including siblings and close relatives. Uncontrolled epilepsy is another extreme where families find it challenging to balance quality of life with uncertainties from seizures.

The current understanding in pediatric epilepsy has improved the standard of diagnosis, investigations and appropriate treatment. The benefits overflow in improving the awareness and acceptance of such a diagnosis in the society in areas such as learning and employment opportunities. The concept of epilepsy syndrome or named epilepsies helps prognostication in a child or adolescent who fits a particular type. Despite these aspects, there is a wide gap in children with intractable epilepsy where effects are far reaching and difficult to quantify. It is becoming clear that in addition to overt clinical seizures, the impact of subclinical seizures and in select circumstances, recurrent seizures may produce brain damage.

Thus, a compelling case arises from arguments above that every effort should be made in achieving appropriate seizure control and seizure prevention. The first step in the management is arriving at the right diagnosis of epilepsy. It is important to distinguish a seizure from a seizure mimic. Clinical history and witnessed information are invaluable to a diagnosis. It is always vital to consider clinical and diagnostic information complementing each other in confirming the diagnosis of epilepsy. Empirical treatment solely based on investigations alone without clinical correlation should be discouraged as an approach to establish a diagnosis of epilepsy.

The decision to treat recurrence of seizures has to be addressed at two levels. The decision becomes almost imminent in an acute case scenario while such haste should be avoided to give way for a well-thought and a sound judgment for long-term daily treatment. A child presenting with an explosive onset of seizures recurring in clusters over a short period of time or as status epilepticus needs immediate treatment to stabilize and break the vicious pattern of recurring seizures. The goal and outcome is cessation of seizures in the short-term. The question of long-term daily treatment follows after control of seizures in the short-term or when a seizure recurs for the second time or beyond weeks or months after the first event. The decision to daily treatment in the long-term should consider issues well beyond epilepsy.

The management of epilepsy is an ongoing contract between the clinician, the child and the family to ensure appropriate quality of life as prior to diagnosis. The access to medical information, social networking and parent groups are freely available on the internet to parents and caregivers in this digital age. There is another section of the society who carries the social stigma of a diagnosis of epilepsy in their everyday life due to false beliefs and being in a disadvantaged background. They lack awareness that pediatric epilepsy is a treatable diagnosis. It is the duty of the clinician to explore and highlight relevant information to families that may be applicable in a child. In situations, where relevant for e.g., in choosing the right antiepileptic drug (AED) between two or many equally good choices, in making a decision to treat or not to treat in mild or infrequent epilepsies or in agreeing to a decision to wean, it is often helpful in arriving at an informed decision including the views of parents and the child.

GENERAL PRINCIPLES IN PRESCRIBING ANTIEPILEPTIC DRUGS

Decision to Treat or Not to Treat
The decision to treat is based on a firm diagnosis of epilepsy. The first event experienced or witnessed may point to a diagnosis of seizure or the actual type of seizure, focal or generalized and even a named epilepsy syndrome. Such a scenario facilitates early decision to treatment, choosing the right AED and offering prognosis on the seizure outcome. On the other hand, arrival of diagnosis especially of epilepsy syndrome or even the type of seizure is not uncommon to be delayed until very late in the course. Such scenarios can lead to overdiagnosis or misdiagnosis. This can result in unnecessary treatment or even delay in treatment.

The decision to treat is straightforward in epilepsy syndromes such as childhood absence epilepsy (CAE), benign focal epilepsy in childhood and juvenile myoclonic epilepsy (JME), etc. to name a few. The decision to treat should be offered in scenarios where the seizures are characterized by seizure types such as absence seizures, focal or generalized seizures and not necessarily only when an epilepsy syndrome is evident. Infrequently, the decision to treat may arise even after a single unwitnessed seizure based on safety. Events of unwitnessed nature on more than two occasions may mandate a decision to treat without the seizure being characterized adequately. The arguments in above scenarios to treat are valid as long as adequate care has been taken. In circumstances, where a seizure mimic cannot be excluded, it is useful to investigate further than accepting to treat.

The decision not to treat is much more complex and is based on several reasons. It is valid in seizures or epilepsy type where the natural course is predictable with a low recurrence risk and a high chance of remission. The merits and demerits of treatment to influence risk recurrence versus side effects may not favor one to another. These facts are very much true in children with febrile convulsions and benign epilepsy syndromes in the neonatal period, infancy and childhood. It is very common for children not to be treated in the above scenarios. A more complex scenario arises in children with developmental delay where mild seizures occur in the context of intercurrent illnesses. A decision to wait and not treat is acceptable if the implications are discussed with the family.

The decision to *treat* or *not to treat* a patient with a single unprovoked seizure is controversial. Wait and watch policy is appropriate in most of the cases and anticonvulsant drugs may be started after the second episode of seizure. By this approach, 50% of patients who are never going to have the second seizure are not unnecessarily treated with AED for 1–2 years period. Evidence shows that immediate treatment with an anticonvulsant drug reduces the risk of a subsequent seizure in the short-term, but does not alter the long-term outcome.

Treatment of a first unprovoked seizure must also include education and anticipatory guidance to patients and families.

Usual topics discussed are recurrence risk, risks versus benefits of anticonvulsant drug initiation, injury prevention, first aid, school considerations and recreational activities. There is no need for any activity restriction and child should be allowed to be his or her usual self. Helmet use for bicycling, restriction of climbing on heights and supervised swimming is recommended. For those who are found to have photosensitive seizures, we recommend avoidance of provocative lighting as far as possible, patching of one eye (photosensitivity is a binocular phenomenon and the incidence of seizures can be reduced by patching one eye at a time) and wearing glasses with special filters.

Mechanism of Action of Antiepileptic Drugs

Most AED medications have one or more mechanism of actions. A simple basis of understanding AED mechanism of action is their ability to facilitate or inhibit neural transmission at the level of ion channels or neuron receptors. The most important among the ion channels and receptors are sodium and calcium channels, gamma-aminobutyric acid (GABA) and glutamate receptors respectively. A rule of thumb is AEDs with sodium channel blockade are effective against partial seizures while AEDs with calcium channel blockade are effective against absence seizures.

The sodium channel blockade is the most common pathway for several AEDs including phenytoin, carbamazepine, oxcarbamazepine, lamotrigine, valproate, topiramate, rufinamide, lacosamide and zonisamide. The well-known calcium channels of T-type in the thalamic area are blocked by valproate, ethosuximide and zonisamide and hence appropriate medications in absence seizures. GABA activation is best seen with phenobarbitone and benzodiazepines.

Newer and third generation AEDs such as lamotrigine, topiramate and levetiracetam have multiple mechanisms of action. Lamotrigine inhibits voltage gated sodium and calcium channels. Topiramate inhibits sodium channel and glutamate transmission while enhances GABA activation. Levetiracetam inhibits calcium channel and glutamate transmission while enhances GABA activation.

Prescribing the First Antiepileptic Drug

The choice of first AED in majority of instances can be straightforward and specific to the type of epilepsy or epilepsy syndrome. In others, they can become complicated by other factors. These may be factors relevant to an individual patient such as age of the subject, e.g., neonate, child or adolescent, body weight and comorbid diagnosis, factors relevant to medication such as pharmacokinetics, side effects or drug interaction and factors relevant to social issues such as treatment costs to the family.

The choice of first AED in neonatal seizures are narrower than other age groups given that tolerability and safety profile for many of the available agents are unknown in this age. Beyond two years of age, the choice of valproate or carbamazepine for generalized or focal seizures respectively may be the first step. In select situations, the first AED chosen may be one of the new and broad spectrum AED. For example, Lamictal may be chosen in preference to valproate in a child or teenager who is overweight or at risk of gaining weight. Learning and attention difficulties at school may be a factor in deciding against carbamazepine. Ease of introducing and need for rapid escalation of AEDs may narrow choices to those that can be administered by both parenteral and oral routes such as valproate or levetiracetam. The cost of AED also has to be factored keeping the family income in mind to improve compliance and affordability in the long-term with option such as phenobarbitone.

Introducing First Antiepileptic Drug

The rule is starting AEDs on low and slow dose for a new onset diagnosis of epilepsy in non-emergent situations. The commencement is made at the starting dose with increases made every few days or on a weekly basis to titrate to the low maintenance dose range aiming for seizure control. Further increases to maximal doses will be guided by seizure control or emergence of side effects. Monitoring drug levels are often useful to ensure therapeutic levels and confirming medication compliance. Drug levels achieve therapeutic range after a single intravenous administration of loading dose or following five half-lives of oral administration of maintenance doses. A quick therapeutic level is desirable in emergency situations with status epilepticus or multiple clustering of seizures. Systematic measurement of drug levels every 3 or 6 months is not mandatory for all patients. Some practical examples for drug level estimation are in unexplained breakthrough seizures, emergence of side effects, and medication doses being outgrown during growth spurts in an adolescent.

Treatment Failure with First Antiepileptic Drug

Failure to control seizures with the first AED is one of the important determinants to the outcome of epilepsy treatment in the short and long-term. The failure to first AED should be addressed by revisiting history and clinical examination, and ensuring written communication have been understood regarding dose and timing of medication. The failure to control may relate to factors that are easily remediable such as dosing errors, inadequate dosing or choosing the right drug formulation. The failure to first AED after exclusion of remediable factors mandates reviewing of home videos or recording seizures by long-term video-electroencephalography (EEG) recording towards confirmation of seizure or epilepsy syndromes as the distinction between age-related, benign epilepsy syndromes from difficult to control or refractory seizures may emerge at that point.

The failure of first AED to control seizure may manifest at any stage of treatment. Breakthrough seizures may occur after a period of adequate control that may responds to dose titration but further increases may prove unsuccessful. A stepwise approach would be to consider alternative monotherapy in place of the first agent. The second AED agent is titrated up while making no changes to the first AED. Once appropriate seizure control is achieved the first AED may be weaned gradually. It is not uncommon that weaning of first AED may result in seizure relapse indicating that the combination may be necessary. Less frequently, the epilepsy may manifest within the first few days to weeks with such severity that there is a need for alternative monotherapy or combination therapy and early polytherapy becomes necessary. Early polytherapy may be anticipated and discussed with families even at diagnosis in epilepsy syndromes such as Dravet syndrome, Lennox-Gastaut syndrome or Doose syndrome.

Pharmacodynamic interaction A synergistic interaction of valproate and lamotrigine is well known. Valproate levels are reduced by phenobarbital, phenytoin and carbamazepine. The latter three AED levels are increase by valproate. Carbamazepine is an enzyme inducer and reduces levels of phenytoin, valproate and lamotrigine.

Decision to Wean or Stop Antiepileptic Drug

Overall about two-thirds of children with epilepsy will remain seizure free during and after the withdrawal of an AED on completing the minimum treatment period for 2 years or more. The majority of seizure recurrences occur within the first year, during or soon after AED discontinuation.

Among several factors, the specific epilepsy syndrome is often the main determinant to predict the duration of therapy and the risk of seizure recurrence occur after discontinuing the AED than the choice or duration of the AED.

This is best illustrated by AED withdrawal after successful completion of 2 years of treatment in patients with age-dependent syndromes given the low risk of recurrence with benign epilepsy in infancy and childhood. On the other hand, AED withdrawal should be deferred for several years or even indefinitely in symptomatic epilepsy or some patients with JME.

Seizure and EEG remission is also an important determinant for AED withdrawal in children with epilepsy as both these factors are desirable outcomes to be attained after the required period of treatment and may predict low risk of recurrence.

Antiepileptic drug withdrawal can be uncertain and may be considered high risk in children with epilepsy whose seizure control was late and difficult to achieve only after institution of alternative monotherapy or polytherapy. In such circumstances, drug withdrawal may prove to be inadequate in children with well controlled seizures leading to seizure relapse. Treatment resumption after a seizure relapse is likely to restore the previous seizure control in the majority but failure to achieve previous seizure control in some can become a major issue. The uncertainty that another AED may or may not work should be explored and the benefit versus risk of drug withdrawal needs to be discussed with the family.

Refractory Epilepsy

Refractory seizures in children are challenging in diagnosis and management. The use of phrase *refractory epilepsy* is very often used interchangeably with intractable epilepsy. The most simple and practical definition for refractory epilepsy is failure of two AED treatment at maximum tolerated doses with least side effects for a period of 2 years and a referral to a specialist epilepsy center encouraged. It is not unusual that such a diagnosis is arrived earlier in the initial few months and referral to a specialist center is encouraged for further evaluation. The available prediction models in children with refractory seizures are few and inadequate. This is exemplified by the fact that children who turn out with a poor epilepsy outcome do not begin so at start of epilepsy. On the other hand, children with epilepsy who started with poor control later achieve better control.

ANTIEPILEPTIC DRUGS

The starting and maintenance doses along with the non-serious, common and serious side effects are summarized in the **Table 1**. The updated ILAE evidence review of AED efficacy and effectiveness as initial monotherapy for epileptic seizures and

Table 1 Dosages and side effects of antiepileptic drugs

Antiepileptic drug	Starting dose (mg/kg/day)	Maintenance dose (mg/kg/day)	Number of doses	Nonserious side effects	Serious side effects
Carbamazepine*	4	20–30	2–3	Somnolence, weight gain, hyponatremia, transient leukopenia	SJS, agranulocytosis, aplastic anemia, liver toxicity
Clobazam#	0.25–1.00	0.5–1.0	1–3	Somnolence	Tolerance
Clonazepam#	0.05	0.1–0.2	2–3	Somnolence	Tolerance
Ethosuximide	10	20–30	1–2	Abdominal pain, anorexia	SJS
Phenobarbitone	3	3–5	1–2	Somnolence	SJS
Phenytoin	5	4–10	2	Gingival hyperplasia, coarsening of facies, hirsuitism	SJS
Nitrazepam#	0.10–0.25	0.5–1.0	2	Somnolence	Tolerance; drooling and aspiration
Sodium valproate	10	15–40	2–3	Weight gain, tremor, alopecia	Liver toxicity, SJS
Second and third-generation antiepileptic drugs					
Lamotrigine#	0.5	2–10	2	Somnolence, dizziness	SJS
Lamotrigine with Valproate	0.15	1–5	2	Somnolence, dizziness	SJS
Lamotrigine with enzyme inducers	0.5	5–15	2	Somnolence, dizziness	SJS
Levetiracetam#	5	20–60	2	Somnolence, dizziness	Behavioral issues
Oxcarbamazepine*	5	20–40	2–3	Somnolence, dizziness, hyponatremia	SJS
Topiramate#	0.5–1	2–10	2	Weight loss, hypohidrosis, fever, crystalluria and renal stones	Cognitive dysfunction, word finding difficulty
Vigabatrin* in infantile spasms	50	150	2	Hyperactivity	Visual field defects, retinopathy
Sulthiame	5	5–15	2–3	Paresthesia, insomnolence, anorexia	SJS
Felbamate	15	30–45	2	Vomiting, dizziness, hyperactivity	SJS, agranulocytosis, aplastic anemia, liver toxicity
Gabapentin	5–10	20–60	2–3	Aggression, hyperactivity	
Zonisamide	2	8–12	2	Hypohidrosis, fever, crystalluria	
Stiripentol* in Dravet syndrome	25	50	2–3	Somnolence, weight loss, abdominal pain	
Rufinamide* in LGS	10	30–40	2	Somnolence, vomiting	

* Usually commencing starting dose and increase by the same dose amount every 2–3 days to lower maintenance dose range.
# Usually commencing starting dose and increase by the same dose amount every 7 days to lower maintenance dose range.
Abbreviation: SJS, Stevens–Johnson syndrome.

syndromes in the pediatric age group published in January 2013 summarizes the current position of available agents. The ILAE evidence is compared against recommendations from expert review and guidelines from various bodies in **Table 2**. The updated evidence provides data relevant for children in three seizure types and two epilepsy syndromes. The three seizure types are children with partial-onset seizures, children with generalized onset tonic-clonic seizures and children with absence seizures. The epilepsy syndromes are the benign childhood epilepsy with centrotemporal spikes (BCECT) and JME.

The updated evidence was concluded on data from 64 randomized controlled trials (RCTs) over the last 72 years and 11 meta-analyses. The latest recommendation and treatment evidence available on children with absence seizures mirror existing or standard practice of treatment in this group of children. The recommendation falls short in choosing the ideal agent with established efficacy or effectiveness in children with partial and generalized seizures and the children with epilepsy syndromes namely the BCECTs and JME. However, the study data identifies the availability of several agents for daily practice. It ultimately rests on the individual physician to use them to the best of their experience. Syndrome-based treatment of epilepsy and epilepsy syndromes is already discussed in the previous chapter.

NONPHARMACOLOGICAL THERAPIES

Epilepsy Surgery
Candidacy for epilepsy surgery requires a diagnosis of refractory epilepsy and identification of a surgical substrate that when resected leads to improved seizure control and even complete seizure freedom. Certain etiologies such as focal cortical dysplasia, focal hamartoma in tuberous sclerosis, hypothalamic hamartoma, focal area of gliosis and hemispheric syndromes such as Rasmussen encephalitis and hemimegalencephaly have a high chance of being identified with a surgical substrate for resection than intractable epilepsy from genetic, metabolic and degenerative conditions. Focal cortical resection or lesionectomy, hemispherectomy and corpus callosotomy are some of the commonly performed surgeries.

Ketogenic Diet
The Ketogenic diet (KD) is a dietary treatment altering the ratio of fat to nonfat food in increasing ratios from 1:1 to 4:1 with the aim of maximizing ketone production in a way that improves seizure control. It is effective in all seizure types, generalized and partial and a trial of 3–6 months is considered adequate to assess efficacy. It is indicated as one of the treatment options very early in Doose syndrome and in refractory seizures related to Dravet syndrome, Rett syndrome, migration disorders and tuberous sclerosis complex. The diet is carefully prepared by an experienced dietician supervised by the neurologist. This involves a highly motivated child and family who can perform daily ketone assessment in the urine and blood. The side effects are reduced palatability, weight loss, dehydration and nutrient deficiency in the short-term and risk of kidney stones and fatty liver in the long-term. In responders with KD, a 50% seizure reduction in 33% and complete seizure control in 15% is achievable in children who have refractory seizures.

Table 2 Comparison of recommendations for the treatment of pediatric epilepsy

Seizure type or epilepsy syndrome	FDA approved	SIGN (2003)	NICE (2004)	AAN (2004)	ILAE (2013)	Pediatric expert consensus survey (North America 2005)	Pediatric expert consensus survey Europe 2007	Expert committee on pediatric epilepsy, Indian academy of pediatrics 2009
Partial-onset	PB, PHT, CBZ, OXC, TPM, LTG, LEV	PHT, VPA, CBZ, LTG, TPM, OXC, VGB, CLB	CBZ, VPA, LTG, OXC, TPM	A: OXC; B: none; C: CBZ, PB, PHT, TPM, VPA, VGB; D: CLB, CZP, LTG, ZNS	OXC, CBZ	OXC, CBZ	OXC, CBZ	OXC, CBZ, LTG
Bcect	None	Not specifically mentioned	CBZ, OXC, LTG, VPA	A, B: none; C: CBZ, VPA; D: GBP, LEV, OXC, STM	OXC, CBZ	OXC, CBZ	VPA	CBZ, VPA
Childhood absence epilepsy	ESM, VPA	VPA, ESM, LTG	VPA, LTG	A: ESM, VPA, B: none; C: LTG; D: none	ESM	ESM	VPA	VPA, LTG
Juvenile myoclonic epilepsy	TPM, LEV, LTG	VPA, LTG, TPM	VPA, LTG	A, B, C: none; D: TPM, VPA	VPA, LTG	VPA, LTG	VPA	VPA, LTG, PB
Lennox-Gastaut syndrome	TPM, LEV, LTFLB< TPM, LTG	Not specifically mentioned	Not surveyed	Not reviewed	VPA, TPM	VPA, TPM	VPA	VPA, CBZ, LTG, TPM
Infantile spasms	None	Not specifically mentioned	ACTH, VGB	Not reviewed	VGB, ACTH	VGB, ACTH	VGB	ACTH, Oral steroid, VGB

ILAE recommendations are listed according to levels of evidence. Level A: >=1class I randomized controlled trial RCT or >=2 class II RCT; Level B: 1 class II RCT; Level C: >=2 class III RCTs; Level D: 1 class III RCT or >=1 class IV study.
Abbreviations: AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid.
Adapted from Wheless JW, Clarke DF, Arzimanoglou A, et al. Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord. 2007;9:353-412.
Adapted from Naik N, et al. Guidelines for Diagnosis and Management of Childhood Epilepsy. Expert Committee on Paediatric Epilepsy, Indian Academy of Pediatrics, Indian Pediatr. 2009;46:681-98.

Vagal Nerve Stimulation

Vagal nerve stimulation is a treatment in refractory epilepsy those who are not amenable to surgery. With its minimal adverse side effects (hoarse voice, throat pain, cough and headache), lack of pharmacokinetic interactions with drug therapies, negligible compliance issues and improvement in quality of life, the VNS therapy is useful in one third to one half of children in reducing the severity and frequency of seizures in short-term studies.

PROGNOSIS

Seventy percent of children with epilepsy, who are seizure-free for 1–2 years on anticonvulsants, can successfully stop their medications. Specific epilepsy syndrome diagnosis may be helpful in predicting the success or failure of discontinuing anticonvulsant treatment. Around 15% of childhood epilepsy syndromes (e.g., benign rolandic epilepsy, Panayiotopoulos syndrome) always remit. 10% of syndromes (e.g., Ohtahara syndrome, Dravet syndrome, Lennox-Gastaut syndrome, JME, reading epilepsy) usually never remit. For the rest 75% of childhood epilepsy syndromes, the prognosis is intermediate—some patients remit and some do not.

Children with epilepsy are at five times higher risk of dying as compared to the general population. The causes may include direct complication of seizure (e.g., aspiration, arrhythmia), accident, co-morbidities, suicide or sudden unexpected death in epilepsy (SUDEP). SUDEP is rare in children with epilepsy. The adult studies have identified many risk factors for SUDEP and include high seizure frequency especially generalized tonic-clonic seizures, polytherapy, early onset of epilepsy (< 15 years) and associated intellectual disability.

MORE ON THIS TOPIC

Aneja S, Sharma S. Newer anti-epileptic drugs. Indian Pediatr. 2013;50:1033-40.

Chiron C, Duchowny M. Treatment strategies. Handb Clin Neurol. 2013;111: 727-39.

Expert Committee on Pediatric Epilepsy, Indian Academy of Pediatrics. Guidelines for diagnosis and management of childhood epilepsy. Indian Pediatr. 2009;46:681-98.

Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54:551-63.

Hussain S, Sankar R. Pharmacologic treatment of intractable epilepsy in children: a syndrome-based approach. Semin Pediatr Neurol. 2011;18:171-8.

Mikati MA. Treatment of Seizures and Epilepsy. In: Kliegman: Nelson Textbook of Pediatrics. 19th ed. Saunders; 2011. pp. 2025-33.

Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol. 2008;7:57-69.

IN A NUTSHELL

1. Presumption of a seizure diagnosis without considering mimics in a paroxysmal event with loss of consciousness can lead to over diagnosis of seizures.
2. The frequency, intensity and duration of individual seizures in an untreated epilepsy almost always progresses or evolves with time making it unlikely for a diagnosis of epilepsy to be overlooked over months or years.
3. Focal onset of a seizure in unwitnessed or partially witnessed seizures can be easily overlooked. Careful history, home videos and documenting seizures during video electro-encephalography (EEG) recording should be considered during evaluation.
4. Valproate is a safe first antiepileptic drug (AED) choice in children with afebrile seizures over 2 years of age. It is also a useful choice when partial seizures cannot be distinguished from absence seizures in young children.
5. Empirical trial of AED treatment for 3–6 months should not be used as a short cut approach to diagnose epilepsy.
6. Routine and monthly blood test for drug levels, progress EEG's are to be avoided unless the investigations are meant to recommend a change in management.
7. The balance of improved seizure control by frequent and aggressive drug titration should be weighed against exacerbation of dose related side effects. The drug effectiveness in a given patient should be considered individually than drug efficacy.
8. The evidence based management can be used as a framework in the treatment of pediatric epilepsy but should be individualized to a patient by the clinician considering the seizure type or epilepsy syndrome, age, comorbidity and the social circumstances.

Chapter 42.10
Febrile Seizures
Sangeetha Yoganathan

Febrile seizure is a seizure accompanied by fever, without CNS infection, that occurs in infants and children between 6 months and 60 months of age and the documented temperature during febrile seizures should be at least 37.8°C. It occurs in 2–14% of all children worldwide and is also the most common convulsive event in children younger than 60 months. Data from United States found an incidence of one-half million febrile seizure events occurring per year. Peak incidence has been reported around 18 months of age. Reported incidence of febrile seizures from a home based survey in a South Indian state was up to 10%. In children undergoing surgery for drug resistant temporal lobe epilepsy, nearly three fourths have a history of febrile seizures in childhood.

ETIOLOGY

Febrile seizures can occur with febrile events following bacterial or viral infections. Most common cause of fever in children is viral and the febrile seizures were more commonly reported in children with infection due to human herpesvirus 6 (HHV-6), influenza, parainfluenza, adenovirus, respiratory syncytial virus and rotavirus infection. Febrile seizures were also documented to occur following vaccination with diphtheria, pertussis, tetanus (DPT) and measles, mumps, rubella (MMR) vaccines.

PATHOPHYSIOLOGY

Febrile seizures do not occur in all children with fever and the exact pathophysiology is not clear. Various possible postulates were put forward to explain the mechanism of febrile seizures which are briefly discussed here:

Rise in temperature Magnitude of the fever does not seem to affect the occurrence of febrile seizures. Some children have febrile seizures with low temperature and these children are at an increased risk of having recurrences due to lower seizure threshold. Hyperthermia can decrease gamma aminobutyric acid A (GABA-A) receptor-mediated inhibition and hence shift the balance towards excitation. This appears to be mediated by reducing GABA release from presynaptic terminals, but hyperthermia may also decrease postsynaptic GABA receptor function. Various other transmitters and modulators including neuropeptide Y antagonist, arginine and vasopressin have also been studied in experimental models.

Inflammatory mediators Tumor necrosis factor α (TNF-α), interleukin (IL)-1α, IL-1β, and IL-6 are the proinflammatory cytokines. IL-1β acts by increasing the release of glutamate from glia and neurons and by decreasing GABA-A receptor-mediated currents. As a result, there is increased excitation and decreased inhibition. There is an increased frequency of allele promoting IL-1β production and also increased levels of IL-1β in cerebrospinal fluid (CSF) in children with febrile seizures.

Genetic factors Genetics of febrile seizures is complex and is continually expanding. It may explain the high risk of febrile seizures in certain families than others. Positive family history was identified in 25–40% of children with febrile seizures. Chromosomes with reported linkages for febrile seizures are 2q, 5q, 5, 8q, 19p, 19q and also are the genes related to neuronal sodium channel receptor.

Hyperventilation-alkalosis In children with fever there is an increase in respiratory rate which could lead to respiratory alkalosis resulting in increased neuronal excitability. The role of this mechanism in the generation of febrile seizures in children is unclear.

Double hit hypothesis Cortical malformations such as focal cortical dysplasias and microdysgenesis can lower the seizure threshold in a child with febrile seizures and can lead to prolonged status epilepticus. On the other hand, a strong association exists between prolonged and focal febrile seizures and subsequent development of temporal lobe epilepsy.

CLINICAL DIAGNOSIS

Diagnosis of febrile seizures is essentially clinical. There are two types of febrile seizures namely simple and complex febrile seizures.
1. *Simple febrile seizures* are defined as primary generalized seizures occurring in association with fever, lasting for less than 15 min and do not recur within 24 hours.
2. *Complex febrile seizures* are defined as focal, prolonged (more than 15 min), and/or recurrence within 24 hours.

History taking and careful clinical examination is needed to exclude meningitis. History with regard to seizure includes detailed elicitation of semiology, duration, frequency and family history of febrile seizures or epilepsy. Focused clinical examination to look for meningeal signs, signs of raised intracranial pressure and focal neurological deficit is mandatory.

Febrile status epilepticus refers to seizures associated with fever and lasting for more than 30 min. It occurs in 5% of all children with febrile seizures and accounts for 25% of children with status epilepticus. The seizures in febrile status epilepticus is usually convulsive and may be generalized or partial onset with secondary generalization. Studies have shown that febrile status epilepticus is more likely to occur in children with family history of epilepsy and in children with premorbid neurological insult.

A multicentric FEBSTAT study prospectively enrolled 199 children with febrile status epilepticus and analyzed the data on the emergency management of febrile status epilepticus. Data analysis found that children with febrile status epilepticus require an early administration of antiepileptic drugs for control of seizures and even with treatment the seizures might persist for a significant period of time. This study concluded that a standard protocol for the prehospital management of febrile status epilepticus is essential as earlier onset of treatment results in better outcome.

Complex Febrile Seizures and Mesial Temporal Sclerosis
Complex febrile seizures and febrile status epilepticus are associated with subsequent development of mesial temporal lobe epilepsy. Various studies have shown that 30% of patients with mesial temporal sclerosis had a history of febrile status epilepticus. One prevailing hypotheses is that febrile status epilepticus can lead to acute hippocampal injury and later lead on to mesial temporal sclerosis. Other hypotheses states that febrile seizures, febrile status epilepticus and mesial temporal epilepsy are different presentations of an injured hippocampus or genetically predisposed.

Retrospective studies from epilepsy centers have found that adults with refractory temporal lobe epilepsy had a history of complex febrile seizures or febrile status epilepticus in childhood. However, population based studies have not confirmed this association. Published data had shown that magnetic resonance imaging performed within 72 hours of febrile status epilepticus has a good predictive ability of later occurrence of mesial temporal sclerosis. Genetic predisposition, febrile seizures after infection with HHV-6 and HHV-7, pre-existing malformation such as focal cortical dysplasia have also been implicated in the development

of mesial temporal sclerosis. Ongoing multicentric prospective studies might solve the existing controversy regarding the association of febrile seizures and mesial temporal sclerosis.

DIFFERENTIAL DIAGNOSIS

In any infant with fever and seizures, the possibilities that are to be considered are febrile seizures and acute pyogenic meningitis. Large retrospective surveys of outcome in children with fever and seizures found that the diagnosis of meningitis in children with febrile seizures varied from 1% to 7%. In children having both fever provoked seizures and unprovoked seizures with a positive family history of epilepsy, consider the possibility of generalized epilepsy with febrile seizures plus (GEFS+). In a normally developing child with infantile onset febrile seizures followed by intractable epilepsy and disturbed psychomotor development, should raise the suspect for Dravet syndrome, an epileptic encephalopathy. Dravet syndrome and GEFS+ are channelopathies with known mutations in the neuronal sodium channel 1A (SCN1A). Children having focal seizures or prolonged febrile seizures, one should screen for an underlying structural pathology like mesial temporal sclerosis or focal cortical dysplasias. L-2 hydroxyglutaric aciduria is a neurometabolic syndrome with frequent febrile seizures as an initial presenting symptom and can later progress to have myoclonus, pyramidal, extrapyramidal and cerebellar signs.

APPROACH TO A CHILD WITH FEBRILE SEIZURES

History taking and meticulous clinical examination is required in all children with febrile seizures. Diagnostic testing is not warranted in most of the cases.

Search for fever etiology Pediatricians should plan investigations in children with febrile convulsions to identify the cause for fever. Complete blood count is done as a part of fever evaluation rather than as a part of routine investigation.

Routine investigations American Academy of Pediatrics (AAP) Subcommittee strongly recommends that testing of routine blood parameters like serum electrolytes, calcium, phosphorus, magnesium, blood glucose or complete blood cell count is not essential in children with febrile seizures.

Role of lumbar puncture Evidence from observational studies recommends that lumbar puncture should be done in any child with fever, seizures and meningeal signs (e.g., neck stiffness, Kernig and/or Brudzinski sign). Lumbar puncture is optional in children aged between 6 months and 12 months with febrile seizures if the child had not received *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae* vaccines, immunization status cannot be determined with an increased risk of bacterial meningitis or pretreated with antibiotics.

Electroencephalography An electroencephalography (EEG) should not be performed in a neurologically healthy child with simple febrile seizures, as it is not only expensive but also increases the parental anxiety. Cochrane review on the utility of EEG in children with complex febrile seizures concluded that there is no evidence to support or refute the use and timing of EEG in these children.

Neuroimaging Neuroimaging should not be performed in the routine evaluation of the child with a simple febrile seizure. Neuroimaging should be done in all children with febrile status epilepticus, neurological examination revealing focal neurological deficit and signs of raised intracranial tension. Magnetic resonance imaging of brain with an epilepsy protocol is essential in children with history of febrile seizures and refractory epilepsy to rule out focal cortical dysplasia and mesial temporal sclerosis.

MANAGEMENT

Antipyretics

Antipyretic agents act by the alteration of prostaglandin synthesis. Elevated levels of prostaglandins E2 and F2α in the CSF have been found to be associated with febrile seizures. Ibuprofen is an inhibitor of cyclooxygenase-1 (COX-1) than COX-2 whereas diclofenac is an inhibitor of both these enzymes. Acetaminophen acts by reducing the prostaglandins E in the central nervous system. Randomized controlled trials have found that the use of antipyretic agents in children with previous febrile seizures were ineffective in the prevention of recurrent febrile seizures. Paracetamol may provide comfort and symptomatic relief, but should not be recommended to prevent further febrile convulsions. Tepid sponging during febrile episodes had been found to be ineffective in preventing the recurrence of febrile seizures.

Acute Management

Airway maintenance, breathing and circulation must be the priority in any child with febrile seizures. Benzodiazepines are used in the acute management of children with febrile seizures. Diazepam (rectal, intravenous), lorazepam (intravenous, intranasal), midazolam (intramuscular, intranasal, intravenous, buccal) have been found to be safe and effective in the control of prolonged febrile seizures in children. Dosages of these drugs are mentioned in the **Table 1**.

Management of Febrile Seizures in Hospital Setting

In most of the cases, febrile convulsions stop spontaneously and in case of failure of seizures to cease spontaneously, maintenance of airway, breathing and circulation are the priorities. Intravenous access should be established and first dose of benzodiazepine is administered. Consider repeating the dose of benzodiazepine if seizures are not controlled. Febrile status epilepticus should be treated as per standard protocol for management of status epilepticus.

Management of Febrile Seizures in Home Setting

During the active seizure episodes, parents should be instructed to remain calm and avoid panic. They should make an observation of the semiology and duration of seizures. Child's clothing should be loosened and the child should be placed in the lateral decubitus position to avoid aspiration of saliva or vomitus. No attempts should be made to administer any drugs or fluids orally. Parents can administer rectal diazepam or intranasal midazolam in case of prolonged seizure lasting over 2–3 min.

Prophylaxis Therapy

Intermittent Prophylaxis

Rapidly acting anticonvulsants are used during the fever episodes in attempt to reduce the risk of recurrent febrile seizures.

Table 1 List of drugs used in acute management of prolonged febrile seizures

Drug	Route of delivery	Dosage
Midazolam	Intravenous	0.2 mg/kg/dose
	Buccal	0.2–0.5 mg/kg/dose
	Intranasal	0.2 mg/kg/dose
	Intramuscular	0.2 mg/kg/dose
Diazepam	Intravenous	0.3 mg/kg/dose
	Rectal	0.5 mg/kg/dose
Lorazepam	Intravenous	0.1 mg/kg/dose
	Intranasal	0.1 mg/kg/dose

Intermittent prophylaxis should be considered only if there are frequent seizures in a short period (3 or more in 6 months; 4 or more in a year) or if the seizures are prolonged for more than 15 min or requiring pharmacological therapy for control. Studies have shown that intermittent clobazam therapy and diazepam prophylaxis had similar efficacy but adverse effects including drowsiness and sedation were lower in children receiving clobazam. The dosage of oral diazepam is 0.3 mg/kg/dose every 8 hourly and the dosage of oral clobazam is 1 mg/kg/day in 2 divided doses for first 48 hours after the onset of fever. There is no evidence for therapies to prevent subsequent epilepsy and to support the prophylaxis for preventing recurrences of simple febrile seizures.

Continuous Prophylaxis

There is evidence that continuous therapy with antiepileptic medications would reduce the risk of recurrences. Sodium valproate is the preferred antiepileptic drug in children with a need for continuous prophylaxis. Phenobarbitone is less preferred nowadays due to the high prevalence of adverse effects on cognition and behavior in these children.

RISK OF RECURRENCE

After the first episode of febrile seizures, 30% of children had one recurrence; 15% had second recurrences and 7% had three or more recurrences. The risk of recurrence was high during 12–24 months of age. Risk factors predicting the recurrence of simple and complex febrile seizures are listed here:

- Early age of onset (< 15 months)
- Epilepsy in first-degree relatives
- Febrile seizures in first-degree relatives
- Frequent febrile illness
- Low temperature at the onset of the febrile seizure.

Children with neurodevelopmental disabilities, family history of epilepsy and complex febrile seizures are at an increased risk of recurrence for unprovoked seizures. The general risk of febrile seizure recurrence is estimated at around 30–40% and the frequency of recurrence is 10% if there are no risk factors, 25–50% if there are 1–2 risk factors and 50–100% if there are 3 or more risk factors. Risk of epilepsy in patients with simple febrile seizures is 1–1.5%. Risk of epilepsy in patients with complex febrile seizures is between 4% and 15%.

EDUCATION TO FAMILIES

The quality of life in parents of children with febrile seizures can be impaired due to fear of recurrences, fear of subsequent epilepsy, apprehension and anxiety during each febrile episodes. Most important step in the management is the counseling of family with children having febrile seizures. Pediatricians must consider the following steps while counseling the family:

- Describe in as much detail as possible the features of febrile seizures and the benign nature of illness.

- Instruct on the need of appropriateness of anticonvulsive therapy, their risks and benefits.
- Verify that the instructions for fever control and domiciliary management of seizures are well understood.

LONG-TERM OUTCOME

Febrile seizures are benign disorders with an excellent outcome and population based studies have shown normal intellect and behavior, even for complex febrile seizures. There is no data showing increased risk for mortality and morbidity in children with simple febrile seizures.

IN A NUTSHELL

1. Febrile seizures are the most common convulsive event in children between 6 months and 60 months.
2. Majority are simple febrile seizures.
3. Diagnosis is essentially clinical.
4. Long-term continuous antiepileptic drugs are not recommended in children with simple febrile seizures.
5. Intermittent prophylaxis must be used in selected cases.
6. Long-term outcome in these children is excellent.
7. Education of caregivers is crucial in the management of febrile seizures.

MORE ON THIS TOPIC

Baumann RJ, Duffner PK. Treatment of children with simple febrile seizures: the AAP practice parameter. American Academy of Pediatrics. Pediatr Neurol. 2000;23:11-7.

Capovilla G, Mastrangelo M, Romeo A, Vigevano F. Recommendations for the management of "febrile seizures": Ad Hoc Task Force of LICE Guidelines Commission. Epilepsia. 2009;50:2-6.

Karande S. Febrile seizures: a review for family physicians. Indian J Med Sci. 2007;61:161-72.

Neurodiagnostic evaluation of the child with a simple febrile seizure. Subcommittee on Febrile Seizures; American Academy of Pediatrics. Pediatrics. 2011;127:389-94.

Offringa M, Moyer VA. Evidence based pediatrics: Evidence based management of seizures associated with fever. BMJ. 2001;323:1111-4.

Offringa M, Newton R. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev. 2012;4:CD003031.

Salehiomran MR, Mahzari M. Zinc status in febrile seizure: a case-control study. Iran J Child Neurol. 2013;7:20-3.

Seshia SS, Prasad AN. Re: Reid AY1, Galic MA, Teskey GC, Pittman QJ. Febrile seizures: current views and investigations. Can J Neurol Sci. 2009;36: 679-86.

Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121:1281-6.

Strengell T, Uhari M, Tarkka R, et al. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Arch Pediatr Adolesc Med. 2009;163:799-804.

Chapter 42.11
Status Epilepticus
Ravindra Arya, Katrina Peariso

Status epilepticus (SE) is a common neurological emergency in pediatric practice. This chapter presents an overview of convulsive status epilepticus (CSE) in children older than the neonatal age group and discusses its definition, epidemiology, management and outcomes with special reference to practice in resource poor countries (RPCs). RPCs are countries classified by the World Bank as belonging to low and middle income groups, and encompass those situated in tropical and subtropical regions. The chapter is focused on early and established SE and refractory SE is reviewed only briefly. The pathophysiology of SE, mechanisms of refractoriness, nonconvulsive SE and details of continuous electroencephalography (EEG) monitoring are not discussed further.

DEFINITION

Status epilepticus can be defined at several levels. Mechanistically, it represents failure of intrinsic homeostatic mechanisms to terminate a seizure after onset, such that it would not resolve without extraneous intervention. From a physiological perspective it represents duration of a seizure sufficient by itself to compromise neuronal survival. Historically, SE has been recognized to be a state without inter-ictal recovery of consciousness to baseline level. This heuristic is reflected in the 1964 definition by the first International League Against Epilepsy (ILAE) classification of epileptic seizures, where SE was defined as a condition when "seizures persist for a sufficient length of time or are repeated frequently enough to produce a fixed and enduring condition". In the 1981 revision also, the lack of inter-ictal recovery formed the basis of the definition of SE: "seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur". From an operational standpoint, the need for specifying such duration criteria for a seizure or a cluster of seizures without recovery of consciousness to baseline was long recognized. Biologically such duration should probably reflect compromised neuronal survival in an otherwise normally perfused and oxygenated brain. Experiments in primates showed that seizures lasting 82–299 min can lead to ischemic cellular changes in certain regions of the brain including hippocampus. Specifically, it was observed that circumscribed damage in the CA1 region of hippocampus could be seen with seizures lasting more than 30 minutes.

Culminating physiological and indirect clinical evidence led Epilepsy Foundation of America's working group to define SE as *more than 30 min of continuous seizure activity, or, more than or equal to two sequential seizures without full recovery of consciousness between seizures*. In the evolution of continued seizure activity, a period of around 30 min seemed to represent a physiological watershed, where systemic complications began to surface and the metabolism switched from aerobic to anaerobic. However, physicians were justifiably hesitant to wait for 30 min before treating the patient with parenteral antiseizure medications. Clinical observational studies in diverse populations supported this view since most of the seizures were found to last less than or equal to 5 min. Hence, a downward revision of the critical duration to define SE began, leading to the current definition where a generalized convulsive SE in adults and children more than or equal to 5 years of age is defined as more than or equal to 5 min of continuous seizures or more than or equal to two discrete seizures without complete recovery of consciousness in between. A concept of serial seizures was introduced for a cluster of discrete seizures with interictal recovery of consciousness to baseline level. Further,

it was recognized that for a majority of seizures occurring in the out-of-hospital settings, it is virtually impossible to ascertain the onset and hence to determine even the approximate duration. Hence the definition of SE was expanded to include any patient who is brought convulsing to the emergency room **(Box 1)**.

As a seizure prolongs beyond 5 min, additional terms are used to describe the phases of evolving SE: early (5–30 min), established (30–60 min), and refractory SE (≥ 60 min). Children younger than 5 years represent a special population where physiological data to inform a duration cut-off are lacking, and the onset of seizure may not be well recognized. Perhaps a longer time frame of 10–15 min can be allowed for the definition, particularly in febrile SE which represents an important subset of this group. The issue of asertaination of seizure onset is further relevant to RPCs and alternative definitions have been proposed, though not well accepted. At present, we believe that the operational cut-off of 5 min or presentation to the emergency facility in active convulsions can be used as criteria for treatment decisions, even in younger children beyond early infancy.

EPIDEMIOLOGY

Worldwide, the incidence of SE shows a bimodal distribution with peaks in infancy and the elderly. A systematic review found the highest incidence of 135–156 episodes/100,000 persons/year in children less than or equal to 1 year of age. Overall, the incidence of SE was found to vary from 3.9 to 38 episodes/10,000 persons/year in children, depending on the inclusion criteria of the individual studies. Particularly, the lower figure was seen in a study limited to generalized CSE. The incidence is expected to be higher in RPCs. A hospital-based cohort study from Africa found that the incidence of confirmed CSE was 35 (95% CI 27–46) per 100,000 children/year overall, and was 52 (21–107) and 85 (62–114) per 100,000/year in children aged 1–11 months and 12–59 months, respectively. Although there is a lack of similar prospective population-based pediatric data from South-East Asia, a retrospective study from India found that SE constituted 6.7% of children admitted to the intensive care unit in a tertiary care center.

CAUSES AND RISK FACTORS

Status epilepticus can be a first manifestation of any disease process leading to acute convulsive seizures or can occur in patients known to have epilepsy. In the pediatric population, prolonged febrile seizures constitute the most common subgroup and account for up to 35% of all episodes of SE. From 16% to 38% of SE episodes have been noted to occur in children with a prior diagnosis of epilepsy, with low antiepileptic drug (AED) levels being the most common risk factor. In developing countries, the causes for SE are different with locally prevalent neurological and systemic infections being significant contributors. In a study from sub-Saharan Africa, 58% of episodes with confirmed CSE were attributable to malaria or malaria-associated febrile seizures. Studies from India have noted acute bacterial meningitis and viral encephalitis to be common underlying etiologies. In a randomized controlled trial (RCT) from India comparing 2 routes of administration of lorazepam, 49% of the episodes of acute convulsive seizures presenting to the emergency room were attributable to neurocysticercosis.

Overall, any pathology which can trigger an acute symptomatic seizure can cause a CSE. This includes neurological and systemic

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BOX 1 **Current operational definition of convulsive status epilepticus in adults and children ≥ 5 years of age**

1. Continuous seizure lasting ≥ 5 min
2. Two or more seizures without inter-ictal recovery to consciousness to baseline level
3. Patient brought convulsing to the emergency health-care facility.

infections, acute vascular events, traumatic brain injury, and immune, metabolic or toxic encephalopathies. Similarly, epilepsies of any etiology can either have SE as their first presentation, or can experience an exacerbation and present as SE. The specific risk factors leading to such an exacerbation are diverse and include decreased levels of maintenance AEDs (caused in turn by lack of adherence, scheduled withdrawal, insufficient dose, interaction with concurrent medications, growth spurt, etc.), intercurrent illness, exposure to a known trigger (e.g., sleep deprivation in case of certain idiopathic generalized epilepsy syndromes), or metabolic decompensation.

Febrile Status Epilepticus

One of most common subgroups of childhood SE, febrile status epilepticus (FSE) is defined as a prolonged febrile seizure that continues for more than or equal to 30 min. FSE accounts for approximately 25% of all pediatric SE cases and over 66% of cases in children less than or equal to 2 years of age in the United States and Europe. In developing countries, FSE is second only to neurological infections as an underlying cause for SE. However, it is sometimes virtually impossible to distinguish an acute symptomatic SE from FSE in a child with neurological infection. While the mortality rates associated with FSE have been negligible, the morbidity associated with the respiratory and hemodynamic compromise is not. In addition, there is a higher rate of developmental delays and subsequent epilepsy amongst patients with prolonged febrile seizures, suggesting potential additional long-term morbidity. In the recent FEBSTAT study, about 10% of children with a single episode of FSE were noted to have changes on brain magnetic resonance imaging (MRI) in the hippocampal region. Follow-up imaging performed on patients with initial MRI changes 1 year after their FSE found that about 86% of them demonstrated hippocampal volume loss and about 71% had obvious hippocampal sclerosis. As hippocampal sclerosis is a frequent substrate in patients with temporal lobe epilepsy (TLE), these results offer supportive evidence linking FSE to the development of TLE.

Another valuable insight into FSE gained from the FEBSTAT study is the direct correlation between the time to initial treatment with benzodiazepines and the overall duration of the seizure. The FEBSTAT study showed that 90% (179/199) of children with FSE required at least 1 medication, and 78% required 2 medications to abort their seizures. In this study, where the median seizure length was 68 min, for every 2.7 min delay in the initial treatment, there was an associated 1.3 min increase in seizure duration. This finding is indirectly supported by another study which noted significantly shorter median seizure times than those seen in the FEBSTAT study (35 min versus 68 min) which were attributed to comparatively shorter emergency medical services (EMS) arrival times, and more children receiving their first medication from EMS in the prehospital setting in Israel than in the United States (55% vs 41%). Both of these studies concluded that more education regarding recognition of ongoing SE and aggressive treatment of FSE in the prehospital and emergency room setting will improve the outcomes for these children. In settings where prehospital care is not readily available or the EMS providers are unable to administer benzodiazepines, early treatment is more challenging. Educating the families of children with febrile seizures regarding when to seek medical attention and providing them with a dose of rescue medication that may be administered, if a seizure lasts longer than 5 min can still make a difference, as 10% of children with febrile seizures are likely to have FSE.

MANAGEMENT

Objectives of Treatment

There are several targets that have to be simultaneously addressed to optimize the outcome of a child with CSE. These include:

support of critical physiological functions (airway, breathing and circulation) to ensure adequate brain oxygenation and perfusion, termination of clinical and electrical ictal activity, identification and management of precipitating factors, and prevention and treatment of systemic complications of SE. In a subgroup of patients with CSE, it is also pertinent to attempt identification and proximate management of the underlying disease process.

Initial Stabilization

This phase of management of a child with CSE is quite similar to that in any other medical emergency, and is better covered in the intensive care literature. The initial goal is to optimize respiratory and hemodynamic function to ensure adequate oxygenation, perfusion and nutrition (glucose levels) of the brain. One of the first targets is to establish a patent airway which can be challenging in an actively convulsing child. Increased tone of mandibular muscles leading to a tightly clenched jaw, obstruction by a swollen or bitten tongue, or extraneous circumstantial factors in some patients can be potential barriers to a successful airway. Proper positioning of the head, oral and nasopharyngeal suction of the secretions, a nasopharyngeal airway and oxygen supplementation via a non-rebreathing mask are the immediate first steps. At this stage, a rapid assessment regarding need for assisted ventilation should be made. The SE itself, the underlying pathology or ongoing drug therapy can cause abnormal and ineffective breathing patterns that should be recognized. Although bag and mask ventilation can be appropriate as a temporizing measure, a rapid sequence intubation is recommended for children with anticipated need for prolonged ventilation, hemodynamic compromise or features suggestive of increased intracranial pressure (ICP). The next step after stabilizing respiration is to obtain good quality vascular access to administer fluids, electrolytes and medications. At least two large bore intravenous (IV) catheters should be promptly established, which can be challenging in an acutely convulsing child because of movements or collapsed veins. Several different nonvenous routes have been tried for the treatment of acute convulsive seizures and SE, which are summarized below. In children less than or equal to 6 years of age, the intraosseous route is another option.

Drug Therapy for Seizure Control

The pharmacotherapy for termination of CSE begins with administration of IV lorazepam (LOR). The efficacy and safety of LOR in different care environments is supported by available evidence. In childhood SE the proportion of patients achieving clinical seizure control within 10 min of LOR administration has been consistently between 60% and 80%. In case of nonavailability of LOR, alternative benzodiazepines for IV administration as the first drug in SE include midazolam (MDZ) and diazepam (DZP). Recently, however, among children aged 3 months to ≤18 years, IV-LOR was not found to be superior to IV-DZP for cessation of CSE for 10 min without recurrence within 30 min. This primary end-point was met in 101/140 (72.1%) in the DZP group and 97/133 (72.9%) in the LOR group, with an absolute efficacy difference of 0.8% (95% CI −11.4% to 9.8%).

There is lack of systematic class I evidence for the management of CSE beyond the administration of the first benzodiazepine and there is considerable variability in practice. A majority of published protocols recommend fosphenytoin (FOS) or phenytoin (PHT) in case FOS is not available, as the second drug in sequence. The choice for third drug, after LOR and FOS/PHT is even more variable. Conventionally phenobarbital (PHB) has been used at this place. However, other choices include valproic acid (VPA), levetiracetam (LEV) and even lacosamide (LAC). Some neurocritical care experts recommend moving on to refractory SE protocols at this stage, i.e., after LOR and FOS.

At all steps of management of SE, the choice of drugs should incorporate patient specific factors, for example, avoiding

additional dose(s) of LOR in children who have already received a benzodiazepine within 1–2 hours of presentation, avoiding VPA in children less than or equal to 2 years already on multiple AEDs, or in those suspected to have an organic acid or urea cycle disorder, or preferring LEV in oncological patients with complex therapeutic regimens in view of lack of drug interactions with LEV. Children known to have epilepsy and already receiving AEDs on a chronic basis, present another management challenge. Particularly in children who are taking one of the medications used for treatment of SE, i.e., PHT, VPA, LEV or LAC, effort should be made to ascertain the adherence and total daily dose. Depending on these factors, the treating physician has to make an assumption about the blood level(s) of the chronic medications, till the reports are available. If the physician believes the drug levels to be appropriate, another drug with a different mechanism of action should be preferred. However, if drug levels are expected to be sub-therapeutic, the same medication can be given often using half the conventional dose.

It is important to have a written protocol for management of CSE which is thoroughly familiar to physicians on the emergency medicine, neurology, neurocritical care, and pediatric intensive care services, and is periodically reviewed and updated. A general protocol is provided **(Flow chart 1, Table 1)**. The clinical pharmacology of drugs used in the management of early and established SE are also reviewed briefly **(Table 2)**. These protocols should be regarded as broad guidelines and must be adapted to the needs and resources of a particular healthcare facility.

Nonvenous Routes
As mentioned above, establishing adequate IV access in a convulsing child is challenging and not always possible. Further, the IV route for administration of initial benzodiazepine is often not feasible in the out-of-hospital setting. Hence, attempts have been made to administer various benzodiazepines [LOR, DZP, midazolam (MDZ)] and paraldehyde (PLD) by nonvenous routes including rectal (PR), intranasal (IN), buccal (BC), and intramuscular (IM) routes. The specific route and drug combinations used in various RCTs have included PR-DZP, IN-MDZ, BC-MDZ, IM-MDZ, IN-LOR and IM-PLD. A Bayesian network meta-analysis has shown IN-MDZ to be superior to other route-drug combinations in terms of following outcomes: proportion of patients with seizure cessation within 10 min of drug administration, and persistent seizure cessation for at least 1 hour after drug administration. Specifically, the proportion of patients with seizure cessation within 10 min of IN-MDZ administration was found to be 90.3% (78.8–97.0%, pooled event rate using posterior distribution with 95% credible intervals). Further, the time to seizure termination after IN-MDZ administration was found to be 2.9 (1.8–4.1) min (pooled effect size, 95% credible intervals) [Arya, unpublished data]. Additionally, a recent RCT has compared prehospital administration of IM-MDZ and IV-LOR by paramedics. At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329/448 (73.4%) of patients who received IM-MDZ compared to 282/445 (63.4%) of those who received IV-LOR, with similar adverse event rates in the 2 groups. In clinical practice, the decision to use a particular route-drug combination is usually determined by availability, ease-of-use, social acceptability and physician familiarity.

CLINICAL EVALUATION
In patients with new-onset SE, a detailed evaluation for the underlying cause is usually deferred till after stabilization and seizure termination. However, once the initial management targets are achieved it is pertinent to obtain a fairly detailed history, usually from family and/or bystanders, and perform a diligent examination to facilitate subsequent work-up.

The specific historical details should include information about any pre-existing chronic diseases, intercurrent illness, fever, head trauma, and any medications that the patient is receiving. Additionally, in patients known to have epilepsy, details of treatment, adherence and exposure to known triggering factors should be elicited. The specific circumstances of seizure onset can sometimes suggest the specific cause, e.g., an envenomation. General examination should include inspection of skin for pallor, cyanosis, icterus, cherry red discoloration, needle marks or any rash. Occasionally, general examination may also reveal stigmata of chronic underlying medical conditions. Systemic complications of status epilepticus are listed in **Table 3**.

The neurological examination should carefully document the level of consciousness. In children, it is often helpful to document the actual activity observed, in addition to a score on a coma scale. The cranium should be evaluated for any evidence of injury including local bruises, edema, bleeding from external auditory meatus, Battle's sign and cerebrospinal fluid otorrhea or rhinorrhea. Cranial nerve exam should focus on pupils and their reactions, fundus oculi, ocular position at rest, spontaneous and elicited eye movements. The occurrence of nystagmus requires fixation, hence, it is a clinical dictum that nystagmus in an unconscious patient represents seizure activity until proven otherwise. Motor examination should look for any asymmetry in posture or spontaneous movements, and decerebrate or decorticate posturing. Evidence for meningeal irritation and raised intracranial pressure (ICP) should be actively sought for. In this regard, absence of papilledema does not conclusively rule out raised ICP in children.

Continuous EEG monitoring and neuroimaging, preferably magnetic resonance imaging (MRI) of the brain are the two most important investigative modalities. It is often valuable to communicate with the radiologist about the specific clinical question(s) that are being sought from the imaging, e.g., contrast administration may be considered to increase the yield for certain infections, or susceptibility weighted sequences may be necessary if hemorrhage is suspected, and so on. Further details of the clinical utilization of these tests and role of other specific investigations are beyond the scope of this chapter.

REFRACTORY STATUS EPILEPTICUS
While there is no standard definition for refractory SE, most care environments and research publications have used variations on the following two criteria: (1) a convulsive seizure lasting longer than 60 min, which may be continuous or intermittent without return to baseline mental status; and/or (2) an acute convulsive seizure that is refractory to more than or equal to two classes of anti-seizure medications. At present, it is believed that the underlying etiologies for refractory SE are similar to those for impending, early and established CSE. However, as has been seen specifically in patients with febrile SE, a treatment delay may lead an established CSE to progress to refractory SE. In this regard, it is pertinent to differentiate refractory SE occurring in a patient with known pre-existing epilepsy from that occurring in the context of an acute encephalopathy. As mentioned earlier, this acute encephalopathy may be traumatic, infectious, vascular, immune, multifactorial, or may remain undiagnosed. Some of these patients with new-onset refractory SE (so-called NORSE) are increasingly being recognized to have autoimmune encephalitis.

Drug Therapy of Refractory Status Epilepticus
At this time, there are no randomized trials to guide treatment recommendations for refractory CSE. However, the two most commonly used regimens in children include continuous infusion of either MDZ or pentobarbital. By the time these coma inducing medications are considered, patient should have been intubated and managed in intensive care unit with skilled ventilatory care. Following is a brief review of some of the medications used in the

Flow chart 1 Management of status epilepticus in children older than 29 days (the protocol developed by Cincinnati Children's Hospital Medical Center Status Epilepticus committee and the Division of Emergency Medicine)

- Establish ABCs (maintain airway, provide oxygen, support vert ventilation as needed)
- Attach patient to monitor and pulse oximetry
- Obtain IV/IO access: Obtain finger-stick blood suger, I-stat and red top (to be sent for AED levels if applicable)
- Correct hypoglycemic, hyponatremia and/or hypocalcemia, as indicated

if having IV/IO access, give lorazepam 0.1 mg/kg push (max 4 mg)
If no IV/IO access, give midazolam 0.2 mg/kg Buccal/IN/IM (max 10 mg)

Seizure abates

Continue close observation
Ensure adequate oxygenation
Manage airway as clinically indicated
Consider I-stat to re-measure PCO_2
Discuss further management with neurology

Still seizing after 5 min

If having IV/IO access, give lorazepam 0.1 mg/kg push
If no IV/IO access, give midazolam 0.2 mg/kg Buccal/IN/IM
Page neurology consult fellow

Still seizing after 5 min

Other considerations:
1. If already received dose(s) of benzodiazepine (s) at home or via EMS; then only give 1 dose in ED before proceeding to fosphenytoin box
2. Valproate is associated with birth defects (pregnancy category D): recommend negative pregnancy test before giving in adolescent females

Consider IV glucose (avoid in patient on ketogenic diet), naloxone or pyridoxine based on clinical scenario if seizure refractory therapy

Strongly consider EEG if concern for subclinical status

Home AED therapy will not change acute management of status epilepticus except for known contraindication(s) for recommended therapies (examples: allergy, fosphenytoin for Dravet's syndrome, IV glucose for ketogenic diet)

Load with fosphenytoin 20 mg/kg IV via infusion over 15 min
(If fosphenytoin contraindicated: valproate 20 mg/kg IV via infusion over 10 minutes or phenobarbital 20 mg/kg via infusion over 20 min)

Still seizing 10 min after infusion is complete

Load with phenobarbital 20 mg/kg IV via infusion over 20 min
(If phenobarbital contraindicated: levetiracetam 50 mg/kg IV via infusion over 5 minutes or valproate 20 mg/kg IV via infusion over 10 min)
Page PICU fellow

Still seizing 10 minutes after infusion is complete

Start pentobarbital 5 mg/kg bolus, then 1 mg/kg/hour IV infusion
Perform endotracheal intubation if not already done

Abbreviations: ABC, airway, breathing, and circulation; AED, antiepileptic drug(s); ED, emergency department; EEG, electro-encephalography; EMS, emergency medical services; IM, intramuscular; IN, intranasal; IO, intraosseous; IV intravenous; PICU, pediatric intensive care unit.

treatment of refractory SE in children with some suggestions for clinical use **(Table 4)**.

Midazolam It acts by positive allosteric modulation of gamma-aminobutyric acid (GABA)-A receptors, is hydroxylated in the liver, and the metabolite undergoes renal excretion. Hence, MDZ levels may be affected by other medications, and hepatic or renal dysfunction. In pediatric case series, it has been found to achieve clinical and electrographic seizure control in 70–95% of instances. There is some evidence that rapid escalation of infusion rate may be more efficacious. Recurrent and breakthrough seizures are frequent (45–65% of episodes). MDZ only rarely induces hypotension by itself.

Pentobarbital It also depresses neuronal excitability by enhancing GABA-coupled responses. It is the first metabolite of thiopental,

which is available itself in some countries. Due to high lipid solubility, it is prone to accumulation with prolonged administration. It is often considered the treatment of choice for refractory SE in advanced care settings, due to significantly lower incidence of short-term treatment failure, breakthrough seizures or need to change to a different medication. Besides respiratory depression, pentobarbital is associated with negative inotropic effect and low cardiac output, causing significant hypotension. Thus, it is imperative to institute continuous blood pressure monitoring in patients on pentobarbital infusion, preferably invasive monitoring via an arterial catheter. Pentobarbital is also associated with increased risk of nosocomial infection, due to an immunosuppressive effect.

High-dose phenobarbital Very high doses of PHB (60–80 mg/kg/day) administered with an objective to attain serum levels more

Table 1 Management approach for status epilepticus

Time (min)	Drug therapy	Medical therapy
0–5	IV LOR (repeat PRN x2)	• Establish A, ensure B & C • IV access • Initiate cardiorespiratory monitoring • Order: Glucose, ABG, Na, K, Ca, CBC, BMP, AED levels • IV dextrose, fluids
5–30 (Early)	IV FOS/PHT	• Continue cardiorespiratory monitoring and support • Initiate CEEG monitoring • Identify and treat ABG/electrolyte disturbances
30–60 (Established)	IV PHB/VPA/LEV	• Identify and treat complications of etiology or SE *per se* • Consider IV pyridoxine in an infant with no obvious cause • Consider empiric antibiotics if febrile • Consider imaging
≥ 60 (Refractory)	MDZ/pentobarbital infusion	• PICU (if not already) • Assisted ventilation, vasopressor support

Abbreviations: A, airway; ABG, arterial blood gases; AED, anti-epileptic drug(s); B, breathing; BMP, basic metabolic panel; C, circulation; CBC, complete blood count; CEEG, continuous EEG; FOS, fosphenytoin; IV, intravenous; LEV, levetiracetam; LOR, lorazepam; MDZ, midazolam; PHB, phenobarbital; PHT, phenytoin; PICU, pediatric intensive care unit; VPA, valproic acid.

than or equal to 1,000 μmol/L, have anecdotal evidence for rapid control of refractory SE in children. Most of the case series report that hypotension was unusual and often mild.

Propofol It is an IV anesthetic that acts by a similar GABA modulation mechanism. It is rapidly acting (burst suppression within 30 min in nearly 70% of instances) and allows easy titration. However, with prolonged administration the terminal half-life may increase to several days. It is often avoided in children due to association with so-called *propofol infusion syndrome* characterized by cardiac failure, rhabdomyolysis, metabolic acidosis, renal dysfunction and sometimes death. Some of the factors reported to be associated with increased risk of this syndrome include: high dose of propofol, prolonged use, co-administration with catecholamines or corticosteroids, and a low body mass index. Additionally, increased mortality has been reported with propofol administration in children on ketogenic diet. Although some recent observations have challenged these concepts, there is reluctance in using propofol in children with refractory SE given that it is not known to be more effective than other medications, but may potentially have higher risks and higher mortality.

Inhaled anesthetics There is limited experience with rapid induction of dose regulated burst suppression using isoflurane and desflurane in children with refractory SE. However, all patients have been reported to develop hypotension requiring vasopressors and several had atelectasis, infections, paralytic ileus, or deep vein thrombosis.

Table 2 Clinical pharmacology of drugs used in the treatment of early and established status epilepticus

Drug	Dose (mg/kg)	Maximum single dose	Adverse effects with acute usage	Comments
Lorazepam	0.1	4 mg	Respiratory depression, hypotension, sedation	May be a delay in the onset of action by upto 2 min Has a redistribution time of 2–3 hours
Diazepam	0.2–0.5	20 mg	Similar to lorazepam	Although the elimination t ½ is ~24 hours, it gets quickly redistributed within 15–20 min For rectal administration, age and weight dependent dosing is used in pediatric patients
Midazolam	0.2–0.3	10 mg	Similar to lorazepam	
Phenytoin	20		Ataxia, nystagmus, dizziness, hypotension, QT prolongation, cardiac arrhythmias, local tissue reaction	Dose-dependent elimination with saturable metabolism, cautious use in children already on maintenance phenytoin Solvent for injection should be glucose free Slow infusion (1 mg/kg/min, up to maximum of 50 mg/min)
Fosphenytoin	20 (measured in phenytoin equivalents)		Rare hypotension	Phosphate ester pro-drug of phenytoin, well absorbed by intramuscular route Can be infused intravenously more rapidly compared to phenytoin, (3 PE/kg/min up to a maximum rate of 150 PE/min)
Valproic acid	15–20		Sedation, hyperammonemia, disturbed liver function	Infusion rate 3–6 mg/kg/min Caution with use in age ≤ 2 years or in women of childbearing age given teratogenic risk
Phenobarbital	20		Sedation, respiratory depression, hypotension	Infusion rate < 100 mg/min Long elimination half-life
Levetiracetam	20			Can be rapidly infused over 5 min Minimal drug interactions
Lacosamide	10–15	200 mg	Cardiac rhythm disturbances including increased PR interval	Limited information on efficacy in status epilepticus Minimal drug interactions
Pyridoxine	100 mg*		Apnea, bradycardia	Used in children ≤ 2 years of age with SE of unknown etiology Given as a bolus under EEG monitoring

*Not mg/kg

Table 3 Systemic complications of status epilepticus

System	Complications
Respiratory	• Apnea (acute apnea after a prolonged seizure without antecedent abnormal breathing pattern may at times suggest a rapidly evolving posterior fossa lesion)
	• Abnormal breathing patterns: may cause ineffective ventilation to the point of respiratory acidosis
	– *Cheyne-Stokes breathing:* Waxing waning hyperpnea, regularly alternating with shorter period of apnea; may be seen in massive supratentorial lesion(s), deep-seated cerebral or diencephalic lesions, e.g., subdural hematomas, infarcts, or meningitis, and certain metabolic disturbances. Important to rule out coexistent pulmonary disease
	– *Central neurogenic hyperventilation:* Suggests a lesion in lower mid-brain and/or upper pons; important to differentiate from hyperventilation due to medical reasons, e.g., Kussmaul breathing of metabolic acidosis
	– *Apneustic breathing:* Usually seen with low pontine lesions, e.g., basilar artery occlusion
	– *Chaotic irregularly interrupted breathing rhythm:* Each breath varying in depth and rate, may suggest a lesion of dorsomedial part of medulla
	• Aspiration
	• Airway compromise (secretions, hypotonia of tongue and/or oropharynx)
	• Noncardiogenic pulmonary edema
Hemodynamic	• Cardiac rhythm abnormalities (bradyarrhythmias seen more often)
	• Cardiac failure
	• Shock
Muscle breakdown	• Myoglobinuria (may cause oliguria or acute tubular necrosis, consider urinary alkalization, if myoglobinuria is detected or serum creatine kinase is more than 10 times upper limit of normal)
	• Hyperkalemia
Electrolyte abnormalities	• Hypoglycemia
	• Hyponatremia
	• Metabolic acidosis
Acute neurological	• Cerebral edema
	• Central hyperthermia

Table 4 Drugs used in the treatment of refractory status epilepticus

Medication	Initial bolus dose	Initial infusion rate	Maximum infusion rate
Midazolam	0.1–0.5 mg/kg	1–2 µg/kg/min	30 µg/kg/min
Pentobarbital	5–10 mg/kg	0.5–1 mg/kg/hour	3 mg/kg/hour
Propofol	2–5 mg/kg	1–2 mg/kg/hour	10 mg/kg/hour
Isoflurane		End-tidal concentration 1–1.2%	End-tidal concentration 5%
Ketamine	1–2 mg/kg	1–2 mg/kg/hour	5 mg/kg/hour
Valproic acid	20–40 mg/kg	5 mg/kg/hour	N/A
Topiramate	No intravenous formulation. Used via nasogastric route from 300 mg/day to 1,600 mg/day		
Levetiracetam	Not used as an infusion. Total dose of 15–60 mg/kg/day is split in 1–2 daily doses.		

Ketamine As a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, ketamine may be effective in refractory SE, when there is GABA receptor endocytosis leading to decreased efficacy of GABA modulating drugs. It may also be neuroprotective by reducing NMDA-mediated glutamate excitotoxicity. Further, it may improve cerebral perfusion by increasing blood pressure due to its sympathomimetic properties, as compared to most other medications used in the treatment of refractory SE which are prone to cause hypotension. However, cerebellar toxicity with prolonged administration is recognized.

Other medications Although not considered as specific treatments for refractory SE, some of the other medications also have variable anecdotal evidence for control of refractory SE in children. These medications include: VPA, TPM, LEV, adrenocorticotrophic hormone (ACTH) and corticosteroids. These medications may be useful in specific clinical situations, particularly where successful intubation is unlikely, as there is lower risk of respiratory failure with these drugs compared to other regimens. Corticosteroids and ACTH may be useful in patients with suspected or proven autoimmune causes for their refractory SE.

Nonpharmacological treatments Dietary and neurosurgical treatments have been successfully tried in selected children with refractory SE. Ketogenic diet is a high-fat, low-carbohydrate diet with proven efficacy in certain inborn errors of metabolism associated with epilepsy and some drug-resistant epilepsy syndromes. It has been tried in children with refractory SE via modified parenteral nutrition solutions or rarely via gastric tube, with limited success. Regarding epilepsy surgery, both resective and palliative procedures have been used in refractory SE with success being driven by patient selection. The principles of presurgical evaluation and surgical decision making are similar to the patients undergoing more deliberate evaluation, and rely on concordance of multiple modalities. If facilities for epilepsy surgery exist, a consultation with an epileptologist is desirable earlier in the management of refractory SE. Further details about epilepsy surgery for refractory SE are beyond the scope of this chapter.

Although controlled hypothermia has been demonstrated to be beneficial in adults after cardiac arrest and neonatal encephalopathy, its role in pediatric refractory SE is not well defined.

Continuous Electroencephalography Monitoring

Children in refractory SE lack easily measurable indices of function and the bedside exam is often unreliable due to the disease process itself and drug therapy. Optimal management of refractory SE requires continuous EEG monitoring, which may not always be feasible in RPCs. It has been shown that EEG detects neuronal dysfunction at a reversible stage providing a therapeutic window. Further, it has been shown that about a third of patients may continue to have electrographic seizures after no clinical seizure activity is obvious. There is both laboratory and clinical evidence that such continued electrographic seizures adversely influence prognosis. If available, patient should be hooked up to the EEG during established or early refractory stages of SE. Regular 21

electrode placement is recommended unless precluded by head trauma. Perhaps the most controversial aspect of the management of refractory SE is the treatment end-point. There is no consensus regarding suppression of only seizures, or suppression of bursts, and if so the degree and duration of suppression. At our institution, we allow for up to 10s of burst(s) every 3 EEG epochs, i.e., 70% suppression, for at least 24 hours and often 48 hours. During this time we review the EEG frequently using both visual analysis and quantitative methods, and modify drug therapy accordingly. Continuous EEG monitoring can also help inform the prognosis with excessive discontinuity or lack of reactivity being suggestive of poor prognosis, whereas progressive EEG improvement with treatment and preserved N2 sleep markers, or evidence of state cycling usually forecasting relatively better outcomes.

Super-refractory Status Epilepticus

When SE continues or recurs despite 24 hours of IV or inhalational general anesthesia, it is termed super-refractory SE. It usually pertains to electrographic nonconvulsive SE noticed on attempting to wean off coma inducing medications. Often, management of super-refractory SE requires continued use of general anesthesia for prolonged periods, at times up to many weeks, with intermittent attempts at weaning under EEG monitoring with simultaneous optimization of maintenance antiseizure medications. Management of concurrent medical complications is complex and individualized. At a minimum, it requires daily attention to pulmonary toilet, fluid management, bowel, bladder and skin care.

Suggestions for Practice

The management of refractory SE in a resource-limited environment should be based on available facilities. In both literature and clinical practice, 2 trends are noticeable: firstly, earlier use of coma protocols often after IV-LOR and FOS; and secondly, preferred use of pentobarbital over MDZ. These trends may not be applicable in most RPCs. Thus, if facilities for adept intensive care are not readily available, there may be value in trying VPA, LEV, TPM or high-dose phenobarbital, before deciding about coma induction. It should be recognized that almost all patients will require some respiratory support during late established or refractory stages of SE. The important consideration at this stage is to prevent hypotension, which can cause secondary brain injury by compromising cerebral perfusion in a setting of sub-optimal autoregulation. Hence, if invasive vascular monitoring and targeted hemodynamic management is not available, MDZ infusion may be tried first, with rapid escalation of infusion rate **(Table 4)**. There should be simultaneous efforts to optimize maintenance antiepileptic drug therapy, because MDZ tachyphylaxis will set-in with continued use. Having attained treatment end-point for 24–48 hours, the infusion should be gradually decreased with continued monitoring for seizures. Again, there is lack of consensus about the management of electrographic seizures seen during this phase. We usually tolerate up to several seizures per day, and do not regard shorter emergent EEG bursts as necessarily associated with poor outcomes. The distinction between refractory SE and SE of shorter duration is the degree of morbidity and mortality associated with the former, which results from a combination of the severity of the underlying disease, the neurological and systemic complications from the prolonged seizure **(Table 3)**, and the adverse effects of the medications needed to control the seizures.

OUTCOMES

Interim Complications

Repeated or prolonged seizures cause several pathophysiological changes that can contribute to morbidity and mortality. In patients with established SE or beyond, it is important to diagnose and appropriately manage these systemic complications **(Table 3)**.

Long-term Outcomes

Status epilepticus is associated with considerable short-term (during hospitalization or within 30 days of SE) and long-term (within 10 years following initial survival 30 days after SE) mortality. Several cohort studies have found age and etiology to be major determinants of both short-term and long-term mortality in SE. A systematic review found mortality to be lower in children as compared to adults and elderly, with short-term mortality up to 9% and long-term mortality up to 7%. Amongst children, infants less than or equal to 1 year of age had the highest short-term mortality, up to 18%. Most deaths during hospitalization for SE or within 30 days of onset of SE have been noted to occur in children with acute symptomatic etiology. In a cohort study from Kenya, 23% of children with confirmed CSE died before discharge, and 18% were left with neurological sequelae. Of the children who died during hospitalization, 75% of the deaths were with 48 hours of onset of SE.

Neurological sequelae of CSE also have been noted to be age dependent with relatively higher incidence in infants. In a large prospective study with mean follow-up of 13.2 months, the incidence of neurological deficits attributable to CSE was 29% in infants less than or equal to 1 year of age, 11% in children 1–3 years of age, and 6% in children more than 3 years of age.

IN A NUTSHELL

1. Status epilepticus in adults and children more than or equal to 5 years of age is defined as: more than or equal to 5 min of continuous seizures, or more than or equal to 2 discrete seizures without complete recovery of consciousness in between, or presentation to the emergency room in active convulsion.
2. Prolonged febrile seizures constitute the most common subgroup of childhood status epilepticus. In resource poor countries, neurological and systemic infections are also significant contributors, the exact nature of infectious agents being governed by local epidemiology.
3. Recent large multicenter study on febrile status epilepticus has shown that delayed initiation of treatment is associated with increased duration of status epilepticus.
4. Several targets have to be simultaneously addressed to optimize the outcome of a child with CSE: support of critical physiological functions (airway, breathing and circulation) to ensure adequate brain oxygenation and perfusion, termination of clinical and electrical ictal activity, identification and management of precipitating factors, and prevention and treatment of systemic complications of status epilepticus. In a subgroup of patients, it is also pertinent to attempt identification and initiate management of the underlying disease process.
5. Status epilepticus is associated with considerable short-term and long-term mortality, with age and etiology being significant predictors of outcome.

MORE ON THIS TOPIC

Bassan H, Barzilay M, Shinnar S, et al. Prolonged febrile seizures, clinical characteristics, and acute management. Epilepsia. 2013;54:1092-8.

Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia.1999;40:120-2.

Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012;135:2314-28.

Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med.1998;339:792-8.

Chapter 42.12
Nonepileptic Paroxysmal Disorders
Hema Patel, David W Dunn

Paroxysmal nonepileptic disorders are frequently encountered in children and can often be mistaken for seizures. Up to 20–25% of patients referred to epilepsy centers with the diagnosis of seizures may have nonepileptic events. It is important to distinguish between paroxysmal events and to avoid inappropriate, expensive evaluations, unnecessary hospitalizations and emergency room visits. An accurate diagnosis can be made for the majority of these cases by a detailed history. Additional diagnostic procedures will usually not be necessary. A classification based on age of onset of these nonepileptic disorders is given in **Table 1** and some of the more common nonepileptic disorders occurring in different age groups are reviewed.

NEONATES AND INFANTS

Tetany

Tetany is characterized by involuntary movements and systemic symptoms and signs. It may be seen in infants near the end of the first week of life that are being fed cow's milk. These infants have hyperexcitability with tremors and muscle spasms. It is due to hypocalcemia and possibly hypomagnesemia. Untreated it may progress to convulsions. Tetany may also be seen in older infants and children. The spasms involve hands characterized by adduction of the thumb and flexion of the fingers (carpopedal spasms) and feet and occasionally laryngospasm. Tapping over the peroneal nerve may cause spasms in the foot and tapping over the facial nerve, contractions in the face (Chvostek sign). Possible etiologies include hypoparathyroidism, renal disease, and vitamin D deficiency.

Breath-holding Spells

Breath-holding spells may be cyanotic or pallid. Cyanotic breath-holding spells are more common. Family history of similar episodes is positive in 23–38%, suggesting a genetic influence, with an inheritance consistent with an autosomal dominant pattern with incomplete penetrance. Details are given in Section 21. Breath-holding spells can be diagnosed based on a history of a precipitating event, which may even be minor, and the characteristic clinical description of the episode. No laboratory tests are needed. A home video of the episode may be helpful. EEG is not indicated unless diagnosis is in doubt and epileptic seizures cannot be conclusively ruled out. If performed, it may reveal slowing or suppression of the background and absence of epileptiform discharges. It is important to differentiate breath-holding from seizures to avoid unnecessary treatment with antiepileptic drugs **(Table 2)**. The brief convulsive movements seen during breath-holding spells are reflex anoxic seizures and are not epileptic.

Shuddering Attacks

Shuddering attacks usually present in infancy at 4–6 months of age, rarely occurring after the age of 3 years. The attacks usually last for a few seconds. They are characterized by rapid tremor or shivering of the body with sudden flexion of head, trunk and elbows, adduction of elbows and knees and no alteration of consciousness. This activity is similar to shivering that occurs when exposed to cold. The episodes occur in clusters, several times a day. The pathophysiology is not known. Differential diagnosis includes infantile spasms or generalized seizures. The EEG is normal. Parents need to be reassured that this is a benign, self-limited condition and no treatment is necessary.

Benign Myoclonus of Infancy

This is characterized by sudden onset of clusters of brief myoclonus or tonic contraction of the head, neck, trunk and extremities seen in developmentally normal infants, 1–12 months of age. The activity resembles infantile spasms, but the neurologic examination and EEG are normal. The etiology is not known. Prognosis is excellent, with the activity usually resolving by 2 years of age. No specific treatment is needed.

Table 1 Nonepileptic paroxysmal disorders classified by age of onset

Age	Disorder
Neonates	Jitteriness Hyperekplexia Benign neonatal sleep myoclonus Tetany
Infants (2 months to 2 years)	Breath-holding spells Shuddering attacks Benign myoclonus of infancy Sandifer's syndrome Spasmus nutans Paroxysmal tonic upgaze of childhood Self-stimulatory behavior Stool-withholding activity Rhythmic movement disorder Hyperekplexia Alternating hemiplegia of childhood
Children (2 years to 12 years)	Stereotypies Tics Parasomnias Migraine and variants [cyclic vomiting, benign paroxysmal vertigo (BPV)] Paroxysmal dyskinesias Gastroesophageal reflux disease (GERD) Self-stimulatory behavior Stool-withholding activity Munchausen by proxy Hypnic jerks
Adolescents (12 years)	Psychogenic nonepileptic seizures (PNES) Syncope Migraine and variants Narcolepsy Tics Paroxysmal dyskinesias Transient global amnesia

Table 2 Differences between breath-holding spells and epileptic seizures

	Breath-holding spells	Epileptic seizures
Triggering factors	Crying, injury	Spontaneous, sleep deprivation, fever
Occurrence in sleep	No	May occur
Description	Provocation followed by apnea and cyanosis or pallor and limpness	Tonic (stiffening) and clonic (jerking) of extremities
Postictal state	Brief	Usually prolonged
EEG	Generalized slowing or suppression of background	Epileptiform abnormalities
Treatment	Reassurance	Antiepileptic drugs

Sandifer's Syndrome

Gastroesophageal reflux disease (GERD) in babies and children may be associated with back arching that occurs after feeding. Sandifer's syndrome is a rare syndrome that was previously described in association with hiatal hernia, but is more commonly associated with GERD. It is characterized by tonic neck extension, deviation of the head to one side (*spastic torticollis*) and dystonic posturing of the trunk. The abnormal posturing is thought to be secondary to discomfort associated with reflux. Onset is usually in infancy or early childhood. This syndrome is differentiated from other causes of torticollis such as posterior fossa tumors, cervical vertebrae abnormalities, or seizures based on its intermittent occurrence with relation to feeding or the postprandial period. The symptoms resolve with treatment of reflux.

Spasmus Nutans

This syndrome is characterized by a triad of head nodding, head tilt or torticollis and nystagmus. It usually begins at 4–12 months of age and remits within 1 or 2 years from onset. Nystagmus is typically horizontal and may be more prominent in one eye. Symptoms may fluctuate throughout the day and are not associated with alteration in level of consciousness. Evaluation should include neuroimaging studies of the brain, because some cases have been associated with lesions in the optic chiasm or third ventricle. No specific treatment is indicated because the condition is benign and self-limiting. Most patients will develop good visual acuity. Subclinical nystagmus may persist until 5–12 years of age.

Paroxysmal Tonic Upgaze of Childhood

Onset is usually in the first year of life, occasionally even in the first few weeks. It is characterized by brief, conjugate upward eye deviation lasting from seconds to minutes with incomplete downward saccades on attempted downgaze and compensatory neck flexion. Horizontal eye movements are normal. These episodes resolve over a few years. Ataxia, learning disabilities, cognitive deficits and pervasive developmental disorder have been reported in some cases. Evaluation is normal including spinal fluid and metabolic studies. Differential diagnosis includes oculogyric crisis, seizures and brainstem disorders. Medications are unnecessary because these paroxysmal episodes are brief and self-limiting and resolve over years. However, ataxia may persist as a permanent disability.

Self-stimulatory Behavior

Self-stimulation is masturbatory behavior that occurs in infants and young children. These are stereotypic episodes of genital self-stimulation, characterized by tightening and rubbing of the thighs with pressure to the pubic and suprapubic area and rhythmic pelvic thrusting. These rhythmic, rocking movements may last for minutes to hours, and are often associated with irregular breathing and flushing, and it may require a lot of effort to distract the child. These episodes may be mistaken for abdominal pain, dystonia or seizures, resulting in unnecessary evaluation. Treatment includes parental reassurance that the episodes are benign and self-limiting. The term *gratification behavior* may be more acceptable because parents may be upset by the term *masturbation*.

Stool-withholding Activity and Constipation

The child may exhibit episodic, abnormal behavior as a way to prevent the painful passage of hard stool because of chronic constipation. It is characterized by sudden interruption of activity with assumption of a motionless posture of slight truncal flexion, occasionally with brief generalized jerks, due to discomfort associated with withholding stool. This behavior may be mistaken for tonic seizures. Treatment of the chronic constipation causes resolution of this behavior.

CHILDREN

Stereotypies

Repetitive stereotyped, purposeless movements are commonly seen in neurologically impaired children with intellectual deficiencies and autism and may be mistaken for seizures. These include rhythmic movements such as head nodding, tongue thrusting, tonic posturing and self-stimulatory behaviors such as rhythmic head shaking, swaying and body rocking. Deaf or blind children frequently resort to self-stimulatory behaviors such as hitting their ears or poking at their eyes.

Other types of stereotypies include more complex motor behaviors with different movements in each episode that are not truly stereotypic. They consist of rhythmic, coordinated, repetitive and quasi-purposeful movements, most commonly affecting the upper extremities and head, such as hand rotation, arm flapping or head nodding. They are brief, lasting from seconds to few minutes, occur in clusters several times a day, are provoked by excitement, stress, fatigue and boredom, and are suppressible. They do not interfere with daily activities and do not occur during sleep. They usually start before 3 years of age. This behavior may not only be seen in children with intellectual deficiencies and autism, but also in those with normal development and intelligence. Comorbidities include learning disabilities, attention deficit hyperactivity disorder (ADHD), tics and obsessive compulsive disorder. Family history is present in 25% of cases. These movements are usually persistent, with resolution only in about 5% by 11–12 years of age. Pathophysiology is unclear. The cortico-striato-pallido-thalamic pathway is thought to be involved.

Diagnosis Stereotypies may be mistaken for tics. Clinical features differentiating the two are listed in **Table 3**.

Management Medications have not been successful in treatment of stereotypies. Behavioral therapy is frequently more successful than medications in controlling these movements.

Tics

Tics are sudden, brief, nonrhythmic, rapid, repetitive, involuntary movements that may be motor, vocal or both. They are associated with a premonitory feeling that is relieved by performing the tic, are aggravated by excitement and stress, and disappear during sleep.

Table 3 Differences between stereotypies and tics

	Stereotypies	*Tics*
Age of onset	Before 3 years	6–7 years
Description	Mostly stereotypic, patterned, predictable	Variable
Location	Arms	Facial muscles
Movements	Flapping, waving of upper extremities	Blinking, grimaces, shoulder shrugs
Rhythm	Rhythmic	Rapid, brief, nonrhythmic
Duration	Prolonged, continuous	Brief, intermittent
Premonitory urge	No	Yes
Triggering factors	Excitement, boredom, stress	Stress, anxiety, relaxation after stress
Suppression	Distraction	Brief, associated with increased urge to perform the tics
Treatment	Poor response	Neuroleptic medications

Efforts to suppress the tics volitionally result in an increasing urge to perform them, with relief after doing so. Motor tics are divided into simple and complex tics and most frequently involve the face, neck, and shoulders. Simple motor tics consist of sudden, brief, meaningless movements such as grimacing, blinking, head jerking, shoulder shrugs and jerks involving the arm or leg. Complex motor tics seem more purposeful, being characterized by activity such as chewing, jumping, hopping, tapping on or smelling objects or self. Vocal tics are also either simple or complex. Simple vocal tics include, throat clearing, coughing and grunting, and complex vocal tics include uttering words or profanities (coprolalia). Tics may be transient or lifelong.

Tourettes syndrome is an autosomal dominant disorder characterized by motor tics and vocalizations present for at least 12 months and is frequently associated with learning disabilities, ADHD, and compulsive behaviors. The disorder tends to be lifelong, though it may stabilize or improve in early adulthood.

Diagnosis Tics need to be distinguished from myoclonic seizures which are characterized by brief, isolated jerks of one or more extremities without associated change in consciousness, are not suppressible, and are associated with epileptiform abnormalities on the EEG.

Management Simple tics that are not disruptive may not require treatment. If they cause distress, effective medications include dopamine antagonist (risperidone, haloperidol), guanfacine and clonidine. Stimulants such as methylphenidate may exacerbate the tics, but may be used at half the usual starting dose without worsening tics in children with tics and ADHD.

Parasomnias

Parasomnias occur during all phases of sleep, including sleep onset (rhythmic movement disorder), non-rapid eye movement (REM) sleep (confusional arousals, night terrors and sleep walking) and REM sleep (nightmares, REM sleep behavior disorder). Rhythmic movement disorder includes head banging (jactatio capitis nocturna), body rocking and head rolling. These are repetitive, stereotypic movements involving the large muscles of the body, occurring during wake to sleep transition and may continue into light sleep. They are seen in infants and young children, peak at 18–24 months of age and usually subside by 5 years of age. They are more common in children with learning difficulties and intellectual disabilities. The bed should be padded to protect against injury. No specific treatment is indicated. However, clonazepam may be used for potentially injurious episodes.

Migraine and Variants (Cyclic Vomiting and Benign Paroxysmal Vertigo)

Migraine headaches are relatively common and may affect approximately 5% of children and 10–15% of adolescents. Some children, adolescents, or parents may be able to identify triggers such as foods, weather changes, menstrual cycle, or sleep irregularity. There are several migraine variants. Benign paroxysmal vertigo (BPV) occurs in preschool age children. These are brief episodes of vertigo without loss of consciousness. The child may fall or hold onto objects for support. Nystagmus may be noted during an episode. Cyclic vomiting presents as episodes of abdominal pain, nausea, and vomiting usually beginning prior to 5–6 years of age. The episodes may last up to 3–4 days and can cause dehydration. Cyclic vomiting may be one presentation of a mitochondrial disorder. Diagnosis and management of migraine are discussed in the chapter on headaches.

Paroxysmal Dyskinesias

These are rare disorders; four types have been described— paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-

kinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED) and paroxysmal hypnogenic dyskinesia (PHD). Majority of the cases are of the PKD and PNKD type and are idiopathic (primary), but may be also be familial or symptomatic (secondary). They present from childhood through early adulthood.

Paroxysmal kinesigenic dyskinesia consists of brief attacks of choreoathetosis, dystonia or ballistic movements, that occur alone or in combination, can be unilateral or bilateral, with retained consciousness, and are precipitated by sudden change in movement or even an intention to move. They may be preceded by an aura of tightness or paresthesia in the involved extremities. The children have a normal neurologic examination between episodes. The condition is more common in boys than girls. It may be familial (autosomal dominant), idiopathic or secondary to conditions such as multiple sclerosis, stroke, or traumatic brain injury. Neuroimaging studies are normal, and no epileptiform changes are noted on the EEG during the episode if the disorder is familial or idiopathic. It responds very well to the antiepileptic drugs carbamazepine and phenytoin. The attack frequency decreases with age with complete remission in approximately 25% of cases.

Paroxysmal nonkinesigenic dyskinesia consists of spontaneous attacks of severe dystonia or choreoathetosis involving face, trunk and extremities, often associated with dysarthria and dysphagia, that may be precipitated by alcohol, caffeine, excitement, stress and fatigue. They last from few minutes up to several hours. Antiepileptic drugs are less consistently effective. They respond to clonazepam and diazepam. Prognosis is not as good as for PKD.

Paroxysmal exercise-induced dyskinesia consists of brief episodes of dystonia that occur after several minutes of exercise and not at initiation of movement as in PKD. The dystonic movement typically involves part of the body doing the most exercise and resolves gradually after cessation of the exercise. Acetazolamide has been effective in some cases.

Paroxysmal hypnogenic dyskinesia consists of brief dystonic episodes during or immediately after arousal from non-REM sleep. These episodes, though included in this classification, are nocturnal seizures seen in autosomal dominant nocturnal frontal lobe epilepsy.

Pathophysiology of paroxysmal dyskinesias is not completely understood. The etiology as with other periodic disorders is presumed to be channelopathies. However, many of the familial cases of PNKD are caused by mutation of myofibrillogenesis regulator 1 (MR-1) gene on chromosome 2, which is not involved with ion channels.

ADOLESCENTS

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures (PNES) are episodic, behavioral spells that can be mistaken for true epileptic seizures. They may be due to an underlying psychological stressor or conflict. PNES have been referred to as hysterical epilepsy, pseudoseizures and nonphysiologic or functional seizures. The term PNES is preferred because it is neutral and not pejorative. PNES have been described extensively in adults but there are fewer reports in children. They account for 3.5–7% of children seen in the outpatient clinic for assessment of seizures. PNES commonly occur between 15 years and 35 years of age, but are seen in all age groups ranging from elementary-age children to the elderly. PNES is more common in females. This preponderance of females is more characteristic in adolescence than childhood. This sex-related trend is even more marked in adults, occurring in 75–80% of the patients.

Clinical features that help differentiate PNES from epileptic seizures are outlined in **Table 4**. In children younger than 13 years

Table 4 Differences between clinical features of psychogenic nonepileptic seizures (PNES) and epileptic seizures

	PNES	Epileptic seizure
Duration	Prolonged	Few minutes
Clinical features	Fluctuating features	Stereotypic
Time of day	Usually while awake with audience present	May occur during sleep
Consciousness during episode	Consciousness retained even with generalized activity Avoidance behavior	Impaired consciousness (except with supplementary motor seizures)
Onset	Gradual, slow escalation in intensity	Abrupt
Head movements	Mostly side to side	Usually head deviation to one side
Extremities	Out of phase movements	In phase movements
Pelvic thrusting	Forward	Retrograde
Vocalizations	Emotional (crying) during episode	Monotonous vocalization at onset
Eyes	Closed during episode	Usually open
Incontinence	Rare	May be present
Tongue bite	Rare, usually on tip	Common, usually on lateral margin
Related injury	Not consistent with fall	Is consistent with fall
Postictal change	Absent or brief, even after prolonged convulsive event	Prolonged with confusion, fatigue, drowsiness (may be absent after frontal lobe seizure)
Affect	La Belle indifference	Concerned

of age, PNES more commonly present as subtle motor activity such as eye fluttering, isolated head shaking, prolonged staring with unresponsiveness, generalized limpness and behavioral changes such as combativeness. In children 13 years and older, the clinical features may be similar to those seen in adults and are characterized by more prominent motor activity with generalized arrhythmic jerking or flailing of extremities, side-to-side head movements and forward pelvic thrusting.

The most commonly identified stressors in children include school difficulties (such as poor school performance, difficulty with learning), family discord (parental divorce, physical abuse, parental or sibling hostility, financial stress), interpersonal conflicts with peers or teachers, bereavement or concurrent personal or family illness. A history of sexual abuse is less frequent in children with PNES than in adults, ranging from 5% to 32% in different reports. Coexisting neurologic illness including headaches, learning disabilities and ADHD have been reported. 10–40% of patients with PNES also have epileptic seizures. Coexistent psychiatric disorders such as depression, anxiety disorders and borderline personality disorders are seen more commonly in adults, though children with PNES have more behavioral and emotional problems, such as mood disorder and anxiety disorders, than children in the general population. The prevalence of psychopathology associated with PNES is higher in the adolescent age group. Family history of epilepsy and somatization may serve as a behavioral model for children to shape expression of their own symptoms.

Diagnosis
It can be difficult to differentiate PNES from epileptic seizures based on clinical features alone. The diagnosis is often delayed for 6 months or more in children and even longer in adults. When the diagnosis is unclear, physicians may start antiepileptic drugs because they worry about not treating a child who might have epilepsy. Misdiagnosis can result in inappropriate and often costly treatment, unnecessary hospitalizations and iatrogenic complications such as invasive procedures in prolonged PNES (e.g., psychogenic nonepileptic status or pseudostatus epilepticus)

and adverse effects from antiepileptic drugs. More importantly, it results in patients not receiving much needed psychiatric treatment.

Evaluation should include a detailed description of the episode by an eye witness. A home video of the events may be very beneficial. Prolonged video-EEG remains the gold standard for definitively diagnosing PNES. A definitive diagnosis of PNES is made only if the recorded event is identified by the family as *the habitual event of clinical concern* and is not associated with epileptiform activity on the EEG. If multiple types of episodes are reported, all these different episodes should be recorded.

Management
It is important to convey the diagnosis to the family in an appropriate, understanding and non-judgmental manner without making them feel that the child is *faking it* or *is crazy*. Early diagnosis is essential to prevent the episodes from becoming the patient's primary coping mechanism for dealing with stress. The patient is referred to a trained mental health professional such as a psychiatrist or psychologist who is knowledgeable about PNES for evaluation and treatment of the underlying psychopathology. The patient is taught new coping skills and stress management techniques. Cognitive behavioral therapy has been found to be beneficial in adults. In some cases with uncomplicated histories, the PNES may resolve after explanation and education about the condition and once the patient and family accept the diagnosis. In patients who were mistakenly placed on antiepileptic therapy, these medications should be weaned slowly. It should be stressed that the physician will continue to maintain contact with the patient so that the family does not feel abandoned.

Syncope
Episodes of syncope are common in adolescents. Most episodes are due to vasovagal syncope caused by brief cerebral hypoperfusion. The episodes occur when the adolescent is awake and standing or, less often, sitting up. They are triggered by a sudden change in posture, pain such as blood drawing, or emotion. Prior to loss of consciousness, the adolescent may notice dizziness, sweating,

nausea, or a feeling of the environment becoming distant. After the event, there may be nausea and fatigue. Syncope may also follow hyperventilation, coughing, or a Valsalva maneuver or after periods of prolonged standing, possibly due to decreased venous return.

Cardiac syncope is less common. These episodes may occur during exertion, are seldom accompanied by symptoms before or after the events, and may occur when the adolescent is lying flat, sitting, or standing. Cardiac syncope may be the result of outflow obstruction, arrhythmia, or heart block.

Diagnosis

The diagnosis is based on the description of the episode. Brief myoclonic or clonic seizure-like activity may occur during vasovagal or cardiac syncope, particularly if the duration of syncope is long or if the adolescent is held upright. The triggering event helps distinguish syncope from seizures. If there is any question of a cardiac cause, an ECG should be obtained. EEG is rarely indicated, and should be performed only if there is no clear precipitant.

Management

Reassurance is helpful. Adolescents can also be advised to maintain adequate hydration and to lie down or do isometric muscle contraction for presyncopal symptoms.

MORE ON THIS TOPIC

Friedman NR, Ghosh D, Moodley M. Syncope and paroxysmal disorders other than epilepsy. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Pediatric Neurology; Principles and Practice, 5th ed. Amsterdam: Elsevier Saunders; 2012.pp.905-25.

Lewis D, Ashwal S, Hershey A, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents. Report of the American Academy of Neurology Quality standards Subcommittee of the Child Neurology Society. Neurology. 2004;63:2215-24.

McKean A, Vaughan C, Delanty N. Seizure versus syncope. Lancet Neurol. 2006;5:171-80.

Patel H, Dunn DW, Austin JK, **et al.** Psychogenic nonepileptic seizures (pseudoseizures). Pediatr Rev. 2011;32:e00.

Patel H, Scott E, Dunn D, Garg BP. Non-epileptic seizures in children. Epilepsia. 2007;48:2086-92.

Patel, H, Walsh, LE, Garg, BP. Chapter 13. Common Problems in Pediatric Neurology, Section 1. In: Martin, RA, Bauer D, Moquist DC. Family Medicine Curriculum in Neurology. American Academy of Neurology Website, 2009. From: https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/4.CME_and_Training/2.Training/4.Clerkship_and_Course_Director_Resources/FM_Chp13_Sec1%20v001.pdf. Accessed June 4, 2014.

Pellock JM. Other paroxysmal disorders. In: Wyllie E, Cascino GD, Gidal BE, Goodkin HP. Treatment of Epilepsy: Principles and Practice, 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2011.pp.495-504.

Roddy SM. Breath-holding spells and reflex anoxic seizures. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Pediatric Neurology; Principles and Practice, 5th ed. Amsterdam: Elsevier Saunders; 2012.pp.900-3.

IN A NUTSHELL

1. A detailed history is essential and necessary for the diagnosis of nonepileptic paroxysmal disorders.
2. Laboratory studies are not necessary for the majority of the nonepileptic paroxysmal disorders.
3. Video EEG remains the gold standard for distinguishing psychogenic nonepileptic seizures (PNES) from epileptic seizures.
4. Reassurance of parents is the key management strategy for most of these disorders.
5. Cognitive behavioral therapy may be helpful in PNES and possibly for frequent migraines.
6. Medications are available for treatment of tics, migraine, paroxysmal dyskinesias and parasomnias.

Chapter 42.13

Coma, Raised Intracranial Pressure and Brain Death

Gurpreet Singh Kochar, Suvasini Sharma

COMA

Coma represents severe derangement in consciousness resulting from diffuse and bilateral cerebral dysfunction, or failure of brainstem-thalamic ascending reticular activating system (ARAS). Evaluation of a comatose child requires a systematic approach with immediate evaluation and stabilization of vital functions, followed by appropriate diagnostic and urgent therapeutic interventions to prevent irreversible brain injury.

DEFINITIONS

Consciousness is the state of awareness of self and environment. There are two components of consciousness: (1) wakefulness or arousal, which is mediated by ascending reticular activating system (ARAS) and diencephalon; (2) awareness, which require functioning of both cerebral hemispheres. Evaluation of awareness in infants and children must take into account the age and appropriate developmental level.

Impaired states of consciousness are also sometimes classified as lethargy, stupor and coma. *Stupor* is a state of unresponsiveness from which the patient can only be aroused transiently by vigorous and repeated stimulation. *Coma* is a state of deep, sustained pathologic unconsciousness (lasting > 1 hour) with the eyes closed characterized by the total absence of wakefulness (absence of sleep wake cycles) and awareness. The motor response in comatose child may be variable. *Lethargy* describes state of alertness between alertness and stupor. Describing all the components used in the assessment of consciousness, e.g., eye opening, motor and verbal responses, awareness of self and environment and presence of sleep wake cycles in an individual patient gives better information rather than using these terms (lethargy, stupor or coma).

Coma is typically a transitional state, evolving toward recovery of consciousness, the vegetative state, the minimally conscious state, or brain death. *Vegetative state* is differentiated from coma by intermittent wakefulness manifested by the presence of sleep-wake cycles and sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival.

Minimally conscious state (MCS) is defined as a condition of severely altered consciousness in which the patient demonstrates minimal but definite behavioral evidence of self- or environmental awareness like following simple commands, yes-no response and some purposeful behavior (smiling, reaching out for object).

EPIDEMIOLOGY

The causes of coma are varied and complex, and are affected by geographic distribution, ethnic background and season. The causes can be broadly classified as coma with focal signs (structural brain disease) and coma without focal signs (diffuse brain disease); summarized in **Box 1**. Nontraumatic coma is discussed in this chapter. In developing countries, infection remains the leading cause of acute nontraumatic coma. In a review of 14 studies from resource poor countries (majority from Africa and Asia, including two studies from India), the three most common infections were cerebral malaria, acute bacterial meningitis and viral encephalitis. The most common viral agent reported in India from 1975 to 1999

BOX 1 Causes of coma in children

I *Coma with focal signs (Structural brain disease)*
- Head injury (accidental and nonaccidental head injury)
- Vascular
  - Arterial ischemic stroke or sinovenous thrombosis
  - Hemorrhagic stroke
- Mass lesions
  - Tumors
  - Abscess
  - Others (tuberculoma, hematoma)
- *Infections:* Meningitis (bacterial or tuberculous with vasculitis), Brain abscess
- *Post seizure state:* Todd's paralysis
- *Immune mediated:* Acute disseminated encephalomyelitis

II *Coma without focal signs*
- *Hypoxia-Ischemia:* Cardiac or pulmonary failure, cardiac arrest, shock, near drowning, carbon monoxide poisoning (gas geyser)
- *Metabolic disorders:* Hypoglycemia, hypernatremia, hyponatremia, acidosis, syndrome of inappropriate ADH secretion (SIADH), diabetes insipidus (DI)
- *Systemic infections:*
  - *Bacterial:* Gram-negative sepsis, meningitis, toxic shock syndrome, *Shigella* encephalopathy, enteric encephalopathy
  - Cerebral malaria
  - *Rickettsial:* Lyme disease, Rocky mountain spotted fever
  - *Tuberculous:* Tubercular meningitis
- *Postinfectious disorders*: Acute necrotizing encephalopathy (ANE), ADEM, hemorrhagic shock and encephalopathy syndrome (HSE)
- *Poisoning:* Drugs and toxins
- Systemic illness associated with coma
  - Hepatic encephalopathy
  - Renal failure
  - Diabetic ketoacidosis, hypoglycemia
- Inborn errors of metabolism
  - Urea cycle disorders
  - Aminoacidopathies and organic academia
  - Mitochondrial cytopathy
- Autoimmune
  - NMDAR antibody encephalitis, limbic encephalitis
- Idiopathic status epilepticus (particularly nonconvulsive); acute epileptic encephalopathies (FIRES, fever-induced refractory epileptic encephalopathy in school-aged children).

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was Japanese encephalitis but studies published after the year 2000 identified enteroviruses and chandipura viruses to be the most common. The noninfectious causes of nontraumatic coma reported from various studies included toxic-metabolic (Reye's syndrome, hepatic encephalopathy, diabetic ketoacidosis, uremia), drug and environmental toxins, hypoxic ischemic encephalopathy (HIE), inborn errors of metabolism and autoimmune causes.

APPROACH TO A CHILD WITH COMA

Any alteration in consciousness must be regarded as life-threatening emergency and urgent steps must be taken to prevent permanent brain damage. The evaluation (both clinical and laboratory) and treatment must go simultaneously throughout the acute stage. Serial evaluations with documentation are often required to determine the change in state of the child and to initiate or modify the treatment.

Emergency Management and Stabilization

As in any critical child, the treatment should begin with rapid assessment and stabilization of airway and breathing. The threshold for intubation should be low in comatose patients and if the initial GCS is less than 8 or airway is not maintainable, child should be intubated and mechanically ventilated. Stabilization

of cervical spine is of utmost importance at this point in cases of proven or suspected trauma. PaO_2 should be maintained around 100 mm Hg and $PaCO_2$ around 35 mm Hg.

Vascular access should be quickly established and necessary samples are taken. Hemodynamic instability should be treated. Hypotension should be treated by fluid resuscitation and vasoactive drugs and maintain mean arterial pressure (MAP) in normal range to maintain cerebral perfusion pressure (CPP) at age-appropriate levels. If glucose is less than 60 mg/dL, glucose should be administered as 25% dextrose (2–4 mL/kg) or 10% dextrose (5–10 mL/kg). Ongoing seizures should be treated with benzodiazepines (lorazepam 0.05–0.1 mg/kg) followed by phenytoin or fosphenytoin loading (18–20 mg/kg of phenytoin equivalents).

If there is any evidence of brain herniation or shift, emergent management of raised intracranial pressure (ICP) should be done (sedation, intubation, mild hyperventilation, raising head end to 30 degrees, keeping head in midline and give mannitol or hypertonic saline). Toxidromes should be considered in unexplained coma and administer specific antidotes if indicated.

History

A careful history should be taken with special emphasis on the events leading to onset of coma. Sudden onset of coma in a previously healthy child may be due to trauma (accidental or non-accidental), seizure, poisoning or hemorrhagic or ischemic stroke. Fever suggests an infective cause but may also indicate intracranial hemorrhage, anticholinergic poisoning or heat stroke. Failure to thrive and neurodevelopmental dysfunction before onset of coma, family history, parental consanguinity and recurrent encephalopathy may suggest inborn errors of metabolism. The chief features to be evaluated in history are summarized in **Table 1**.

General Physical Examination

The examination should begin with assessment of vital signs **(Table 2)**. Presence of jaundice is indicative of liver dysfunction. Skin examination gives important clues about trauma (bruises, lacerations), hepatic dysfunction (jaundice, spider nevi), hematological cause (petechiae) or infection (petechiae and purpura in meningococcemia). Hepatomegaly and/or splenomegaly point towards metabolic, hematological or hepatic dysfunction. Examination of head (anterior fontanel, sutures, head circumference, Macewen sign) and spine (dorsal dermal sinus, signs of occult dysraphism) may provide important diagnostic clues.

Neurological Examination

The purpose of neurological examination in comatose child is to assess depth of coma, recognize focal signs and to assess brainstem dysfunction. The key elements of examination providing vital information regarding depth of coma and localization are—level of consciousness, respiratory pattern, brainstem responses (pupillary, corneal reflex, extraocular movements) and motor response of limbs.

Level of Consciousness

The level of consciousness must be assessed at the outset before any sedatives or neuromuscular blockade. After observing the child for spontaneous motor activity, the motor response should be tested by providing adequate stimuli of graded intensity, starting with verbal commands, vigorous shaking and then painful stimuli (at nail bed, temporomandibular joint and supraorbital notch). The stimulus should be tested on both the sides to look for any asymmetry and localization to pain requires the patient's contralateral arm to cross the midline towards the noxious stimulus. Various coma scales

Table 1 History in comatose child

Events leading to onset	Sudden onset suggests trauma, seizure, stroke or poisoning
Fever, headache, vomiting	Intracranial infection (meningitis/encephalitis)
Seizures at onset	Convulsive or nonconvulsive status epilepticus, poisoning (carbon monoxide, organophosphates, camphor, etc.)
Drug or toxin exposure	Enquire for presence of any drugs at home
History of trauma	Also rule out nonaccidental trauma
History of dog bite	Rabies encephalitis
Recent immunizations	ADEM
Recurrent episodes of encephalopathy	IEM, recurrent toxin exposure
Other concurrent systemic illness	For example, jaundice (hepatic failure), pneumonia (hypoxic encephalopathy), diarrhea (dyselectrolytemia), dysentery (*Shigella* encephalopathy)
Past medical illness	Diabetes mellitus, congenital heart disease, renal failure, liver disease
Family history of previous infant/child deaths	IEM, SIDS
Residence of child	Endemic for cerebral malaria, any epidemic of viral encephalitis in neighborhood

Table 2 General physical examination in comatose child

Fever	Sepsis, focal infective process (meningitis, brain abscess), subarachnoid hemorrhage, pontine hemorrhage, heat stroke, drugs (cholinergic drugs)
Hypothermia	Sepsis, drugs intoxication (sedative/hypnotic or opioid), hypoglycemia, adrenal crisis
Tachycardia	Fever, hypovolemic or septic shock, heart failure or arrhythmias, adrenergic response to acute brain insult, intoxications (tricyclic antidepressants)
Bradycardia	Raised ICP, myocardial injury, intoxications (beta blockers, organophosphates)
Hypertension	Hypertensive encephalopathy, compensatory mechanism to CPP in children with raised ICP
Hypotension	Sepsis, cardiac dysfunction, toxic ingestion, or adrenal insufficiency
Pallor	Cerebral malaria, intracranial bleed, hemolytic uremic syndrome
Jaundice	Hepatic encephalopathy, complicated malaria
Rashes	Meningococcemia, dengue, measles, rickettsial diseases
Petechiae	Dengue, DIC with streptococcal, staphylococcal or meningococcal species or Rickettsia
Head and scalp	*Hematoma:* Traumatic/non-accidental injury; dilated veins, full AF, sutural separation, Macewen sign—hydrocephalus
Spine	Dorsal dermal sinus, tuft of hair (occult spinal dysraphism)

Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; DIC, disseminated intravascular coagulation; AF, anterior fontanel.

include essential elements of neurological examination. Most commonly used scale is that developed by Teasdale and Jennett—Glasgow Coma Scale (GCS). The GCS works well for patients aged 5 years and above **(Table 3)**, but below that age, modifications, particularly of the verbal scale, are needed. There have been some limitations in use of GCS. A simple scale, AVPU (alert, response to voice, response to pain, unresponsive) is about as accurate as the GCS and much easier to use. However, no scale is adequate for all patients; hence, the best policy in recording the results of the coma examination is simply to describe the findings.

Respiratory Pattern

After securing airway, one should observe the breathing pattern **(Table 4)**. Respiratory rhythm is generated by a network of neurons that lie in the ventrolateral medulla. The pattern of respiration can give important clues concerning the level of brain damage but are not of much localization value as most of these patterns also occur in metabolic encephalopathies.

Brainstem Reflexes

The important brainstem reflexes of localization value are pupillary response, corneal reflex, oculocephalic reflex, vestibulo-ocular reflex (cold caloric testing) and, gag and cough reflexes. The pupillary light reflex is very resistant to metabolic dysfunction

Table 3 Glasgow coma scale with modification for children and intubated patients

Best eye response			
1	No eye opening		
2	Eye opening to pain		
3	Eye opening to verbal command		
4	Eyes open spontaneously		

Best verbal response			
	Adult version (> 5 years)	Children's modification	Grimace response for preverbal or intubated patients
1	No verbal response	No vocal response	No response to pain
2	Incomprehensible sounds	Occasionally whimpers and/or moans	Mild grimace to pain
3	Inappropriate words	Cries inappropriately	Vigorous grimace to pain
4	Confused	Less than usual ability and/or spontaneous irritable cry	Less than usual spontaneous ability or only response to touch stimuli
5	Oriented	Alert, babbles, coos, words or sentences to usual ability	Spontaneous normal facial/oromotor activity

Best motor response	
1	No motor response to pain
2	Abnormal extension to pain
3	Abnormal flexion to pain
4	Withdrawal to painful stimuli
5	Localizes to painful stimuli or withdraws to touch
6	Obeys commands or performs normal spontaneous movements

Table 4 Respiratory patterns and their localizing value in comatose patient

Type of breathing pattern	Localization/etiology
Cheyne-Stokes respiration: hyperpnea alternating regularly with apnea	Metabolic encephalopathies (hepatic failure, uremia), forebrain or diencephalic dysfunction function (intact brainstem respiratory reflexes)
Central neurogenic hyperventilation	Metabolic encephalopathies, midbrain and pontine lesions
Apneustic breathing—inspiratory pauses	Bilateral pontine lesions (basilar artery infarcts), rarely in metabolic encephalopathies like hypoglycemia, anoxia or meningitis
Ataxic or irregular, gasping respiration	Lower pontine and medullary lesions
Apnea	Ventrolateral medullary reticular formation

and is very important in differentiating metabolic from structural coma. Asymmetric pupils are caused either by disruption of the oculomotor nerve (cranial nerve III) or impairment of sympathetic fibers (Horner syndrome). Topical administration of mydriatics must be ruled out. Pupillary size, shape, symmetry and response to light provide valuable clues to brainstem and third nerve dysfunction **(Table 5)**. The presence of anisocoria in the comatose patient should be as considered evidence of ipsilateral uncal herniation caused by structural lesion unless proved otherwise.

The presence of oculocephalic (doll's eye), oculovestibular, corneal, cough and gag reflexes are indicative of intact brainstem function. Normal response (smooth conjugate movement of eyes opposite to movement of head) to oculocephalic reflex indicate intact brainstem pathway from vestibular nuclei through pontine and midbrain tegmentum. In a comatose child, slow conjugate movement of the eye towards the stimulated side indicates an intact brainstem (vestibular nuclei in medulla to oculomotor nuclei in midbrain and pons connected by medial longitudinal fasciculus). This response should not be confused with direction of nystagmus (fast component opposite to side of cold water; the traditional *COWS* pneumonic) in awake patient. Comatose patients will not have nystagmus (rapid component away from the side of irrigation) and nystagmus indicates intact cortical function (as seen with psychogenic coma).

Eye movements and position are informative but have less localizing value. Spontaneous roving eye movements indicate that the brainstem is intact, whereas skew deviation (vertical misalignment of the eyes) suggests a brainstem lesion. Conjugate gaze deviation to one side generally indicates an ipsilateral hemispheric or contralateral pontine lesion (parapontine reticular formation) or contralateral hemispheric seizure focus.

Table 5 Pupillary responses at different levels of the brain lesions

Anatomical site involved	Pupils size and reaction
Diencephalic, metabolic	Small, reactive
Midbrain, tectum	Midposition, unreactive, spontaneous hippus
Midbrain, tegmentum	Midposition, irregular, unreactive, corectopia (noncentered)
Third nerve or fascicular (uncal herniation)	Large, unresponsive (Unilateral)
Pons	Pinpoint, responsive

Motor Response

The trunk's and limb's position, spontaneous movements and response to stimulation must be observed to look for any focal deficits (suggestive of postictal Todd's palsy or structural abnormality). Decerebrate posturing is indicative of injury to the caudal diencephalon, midbrain or pons. Decorticate posturing suggests supratentorial lesion (hemispheric or thalamic damage), with sparing of structures below the diencephalon. Posturing often indicate brainstem herniation and should not be confused with seizures. Extrapyramidal movements (dystonia, rigidity) may be seen in Japanese B encephalitis, tubercular meningitis, inborn errors of metabolism (glutaric academia I, mitochondrial cytopathy), anti-NMDAR encephalitis and metoclopramide toxicity.

The fundi must always be examined to look for retinal hemorrhages and papilledema. Retinal hemorrhages strongly suggest intracranial hemorrhage and the possibility of child abuse must be considered. Papilledema may be seen early in the comatose state but is rare. Raised ICP is unlikely in the presence of venous pulsations. The absence of venous pulsation is not helpful. Signs of meningeal irritation may be present in meningitis, encephalitis and subarachnoid hemorrhage. Neck rigidity is present in meningitis, tonsillar herniation or craniocervical trauma. The Kernig and Brudzinski signs are more reliable signs of meningeal irritation.

INVESTIGATIONS (BOX 2)

Some investigations are basic and needs to be done on every comatose child and others are tailored as per clues from history and examination.

Neuroimaging

A *cranial CT* is often the first line neuroimaging and should be performed if focal signs are present or raised ICP is suspected. The value of CT in detecting mass lesions, hemorrhage, skull fractures and hydrocephalus is well established. Obliteration of basal cisterns and midline shift on CT are indicative of raised ICP. A contrast study may reveal features of infection in the form of meningeal enhancement, brain abscess or neurocysticercosis. Certain pathologies like early infarcts, encephalitis and posterior fossa structures may be difficult to visualize. Raised ICP is suggested by effacement of sulci, chinked ventricles and effacement of cisterns. In cases with no history of acute trauma, MRI brain is the preferred modality. MRI is superior to CT for the detection of acute ischemic stroke, encephalitis, demyelination in acute disseminated encephalomyelitis (ADEM), traumatic diffuse axonal injury and posterior fossa lesions.

EEG

It is essential in diagnosing nonconvulsive status epilepticus. Continuous EEG monitoring is mandatory under the following situations: refractory seizures; and patients who are heavily sedated, receiving neuromuscular blocking agents, or being treated with barbiturates for increased ICP.

Other Investigations

In cases of unexplained or recurrent encephalopathy, *work-up for inborn error of metabolism (IEM)* must be done, which include blood ammonia, serum and cerebrospinal fluid (CSF) lactate, urine ketones, plasma amino acids and acylcarnitine profile and urine for organic acids. If a specific history is not obtained, and the cause of coma is not apparent (especially in a teenager or toddler) on above investigations, *a toxicology screen* should be done.

Other investigations in unexplained coma include thyroid function tests and *thyroid antibodies* (for Hashimoto encephalopathy) and work-up for central nervous system vasculitis. If there are associated psychiatric manifestations with extrapyramidal features along with seizures, and frequent autonomic instability, *anti-NMDA receptor antibodies* must be done in serum and CSF.

TREATMENT

Management of a child with coma usually proceeds simultaneously with the clinical evaluation. The emergency treatment and stabilization has already been discussed above and treatment of raised ICP and status epilepticus are discussed in appropriate sections. Specific treatment should be directed to suspected underlying etiology.

- In case of acute febrile encephalopathy, broad spectrum antibiotics (ceftriaxone) should be instituted immediately. If viral encephalitis is likely, then samples for polymerase chain reaction (PCR) for herpes simplex virus should be sent and acyclovir should be started. Antimalarials should be started if there is a clinical suspicion of cerebral malaria.
- *Antidotes:* Naloxone should be used in case of suspected opiate poisoning. Flumazenil is useful for benzodiazepine overdosage.
- Steroids are of benefit in ADEM, meningococcemia with shock, enteric encephalopathy, autoimmune encephalitis (anti-NMDAR encephalitis), tubercular meningitis and pyogenic meningitis.
- If metabolic causes are identified, e.g., diabetic ketoacidosis, hepatic encephalopathy, uremia or hyperammonemia, these should be treated appropriately.

BOX 2 Laboratory tests in comatose child

Initial lab tests
- Blood Glucose
- Electrolytes (Na, K, Cl, Ca)
- Arterial blood gas
- Complete blood counts
- Urea and creatinine
- Liver function tests
- RDT for malaria in endemic area
- Blood culture (in febrile encephalopathy)
- CSF (If meningitis is suspected and there is no contraindication):
  – Cell count, Gram stain
  – Protein, Sugar
  – Cultures

Second tier tests
- *Ammonia levels:* Raised in urea cycle disorders, valproate toxicity and hepatic failure
- *IEM screen:* Serum and CSF lactate, urine ketones, plasma amino acids and acylcarnitine profile (TMS) and urine for organic acids (GCMS)
- Toxicology screen
- Anti-NMDA receptor antibodies (especially if psychiatric features and extrapyramidal features)
- Anti-TPO antibodies (for suspected Hashimoto encephalopathy)
- Autoimmune work-up

RAISED INTRACRANIAL PRESSURE

Intracranial pressure is the total pressure exerted by the brain, blood and CSF in the intracranial vault. The Monroe-Kellie hypothesis states that the rigid covering surrounding the brain creates a protected cavity and the volume contained inside remain constant, that is, the sum of the intracranial volumes of brain, blood, and CSF is constant, and that an increase in volume of one component occurs at the expense of other two.

The ICP values vary with age and normal values for ICP in children are not well established. Normal values are 1.5–6 mm Hg for term infants, 3–7 mm Hg for young children and less than 10–15 mm Hg for adults and older children. A sustained ICP value greater than 20 mm Hg is considered clearly abnormal. Values greater than 40 mm Hg indicate severe, life-threatening intracranial hypertension.

CEREBRAL PERFUSION PRESSURE

Cerebral perfusion pressure is the difference between mean arterial pressure (MAP) and ICP (CPP = MAP – ICP). It defines the pressure gradient driving cerebral blood flow (CBF). Increased ICP reduces CBF. Thus, preventing brain ischemia by controlling ICP is of paramount importance. Under normal circumstances, the brain is able to maintain a relatively constant CBF over a wide range of CPP (60–150 mm Hg in adults) by the process of autoregulation. This process is compromised in patients with raised ICP and the CBF becomes pressure passive wherein systemic hypotension can lead to additional ischemic injury. The pediatric guidelines for severe traumatic brain injury (TBI) suggest that CPP more than 40 mm Hg should be maintained and CPP between 40 mm Hg and 65 mm Hg probably represents an age related continuum for the optimal treatment threshold. Recent data in severe pediatric TBI defined age specific threshold for CPP and suggest that CPP goals of 50–60 mm Hg in adults, more than 50 mm Hg in 6–17 years old, and more than 40 mm Hg in 0–5 years old appear to be appropriate targets for treatment-based studies.

HERNIATION SYNDROMES

As ICP increases within the rigid skull, the capacity of vascular and CSF spaces to compensate get exceeded and there is displacement of brain tissue from one compartment to other. An immediate priority is to look for potentially life threatening signs of herniation **(Table 6)**. One needs to carefully look for subtle sensorial changes, respiratory abnormalities and pupillary change. If these signs are present then measures to decrease ICP should be rapidly instituted. Cushing's triad (bradycardia, hypertension and irregular breathing) is a late sign of herniation.

INTRACRANIAL PRESSURE MONITORING

Indications

The association between raised ICP and poor outcome in TBI has been confirmed in various pediatric and adult studies. However, there is still debate regarding usefulness of ICP monitoring in traumatic and nontraumatic coma mainly because of lack of any randomized controlled trials. ICP monitoring is indicted for a patient with GCS score of 3–8 (after resuscitation) with either an abnormal admission head CT or motor posturing and hypotension. Evidence based reviews on use of ICP monitoring in severe traumatic brain injury in children provides strong support for its use. It is been found beneficial for the outcome and in determining a treatment threshold. The role and benefit of ICP monitoring remains unclear in other conditions such as subarachnoid hemorrhage, hydrocephalus, stroke, intracranial infections, and Reye's syndrome. In other brain injuries, such as hypoxic and ischemic injuries, monitoring ICP has not been shown to improve outcome.

Intracranial Pressure Monitoring Devices

The most common methods used for ICP monitoring are intraventricular and intraparenchymal catheters. The gold standard for ICP monitoring is intraventricular catheter or ventriculostomy drain. The ventricular catheter is connected to standard pressure transducer. The reference point for ICP monitor is foramen of Monro, although practically, the external auditory meatus is used as a landmark. The advantages of ventriculostomy catheters are ability to perform external calibration and therapeutic CSF drainage. The disadvantages are difficulty in placement when ventricles are effaced (which is a common scenario in raised ICP) and higher rate of infection than intraparenchymal catheters. The intraparenchymal catheters are easy to insert and have lower risk of infections but the main disadvantage is that it cannot be calibrated in vivo and may show zero drift over time.

Intracranial Pressure Waveforms

Normal ICP waveform consist of three arterial components—percussion wave (reflects the ejection of blood from heart

Table 6 Clinical recognition of herniation syndromes

Type of herniation	Mechanism	Clinical manifestations
Subfalcine or cingulate herniation	Displacement of the brain (typically the cingulate gyrus) beneath the free edge of the falx cerebri	Impaired consciousness, contralateral leg weakness (due to compression of ACA)
Central transtentorial	Downward displacement of both cerebral hemispheres and diencephalon through tentorial notch causing brainstem compression	*Diencephalic stage*: *Symmetrical small reactive pupils, decorticate* posturing, preserved oculocephalic and oculovestibular reflexes, Cheyne-Stokes breathing *Midbrain-upper pons stage:* Midposition unreactive pupils, decerebrate posturing, absent oculocephalic and oculovestibular reflexes, hyperventilation *Lower pons-medullary stage:* Absent spontaneous motor movements (lower extremities may withdraw to plantar stimulation), midposition fixed pupils, ataxic respiration *Medullary stage:* Flaccid, absent pupillary reflexes and ocular movements, irregular or gasping respiration
Lateral transtentorial (Uncal herniation)	Displacement of uncus of temporal lobe over the free edge of tentorium	Impaired consciousness, abnormal respirations, *ipsilateral third nerve palsy* (unilateral dilated pupil, ptosis), ipsilateral *hemiparesis (compression of contralateral cerebral peduncle—Kernohan notch)*
Tonsillar herniation	Increased pressure in posterior fossa causing brainstem compression and downward of cerebellar tonsils and medulla	Impaired consciousness, neck rigidity, opisthotonus, irregular respirations, apnea and bradycardia

Abbreviation: ACA, anterior cerebral artery.

and transmitted to choroid plexus), tidal wave (reflects brain compliance) and dicrotic wave (which reflects aortic valve closure). Under normal conditions, percussion wave is tallest and tidal and dicrotic waves are of decreasing amplitude. When there is raised ICP, cerebral compliance is diminished, which is reflected in increase in peak of tidal and dicrotic waves exceeding that of percussion wave.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE (FLOW CHART 1)

When elevated ICP is clinically evident, the situation is urgent and requires immediate reduction in ICP. The availability of ICP monitors is not universal and should not come in the way of emergent therapy. When facilities for ICP monitoring are available the management is tailored to:

- Maintaining an adequate CPP (> 50 mm Hg in 6–17 years old, and > 40 mm Hg in 0–5 years old)
- Lower ICP to acceptable levels (< 20 mm Hg for children older than 8 years, < 18 for 1–8 years, and < 15 mm Hg for infants). Several medical and surgical options are available to reduce ICP. A stepwise approach is usually followed with the least toxic therapies utilized first and then second tier and more toxic therapies are added if first tier therapies are unsuccessful.

Respiratory Management

The threshold for intubation should be low in a child with altered consciousness. Early intubation should be considered for those children with GCS less than 8, evidence of herniation, apnea or have inability to maintain airway. Intubation should be carried out by trained personnel and should be preceded by adequate sedation and short acting neuromuscular blockade.

Sedation and Analgesia

After intubation and volume resuscitation (managing ABC), sedation, analgesia and neuromuscular blockade are first steps to control ICP. Benzodiazepines (midazolam infusion) and narcotics (morphine or fentanyl) are used for this purpose. Adequate analgesia and sedation is usually preferred over neuromuscular blockade, as it is quickly reversible and allows for neurological monitoring. If sedatives are not completely effective, then a neuromuscular blocking agent (e.g., pancuronium, atracurium, vecuronium) may be required. However, continuous EEG monitoring and ICP monitoring is recommended with the use of neuromuscular blockers.

Position

The other first tier therapy is mild head elevation of 15–30˚. The child's head is positioned midline with the head end of the bed elevated to 15–30˚ to encourage jugular venous drainage. One has to ensure that the child is euvolemic prior to placing in this position.

Fluid Management

Normovolemia should be maintained by fluid resuscitation with isotonic saline if needed. Hypotonic solutions should not be used. In CPP directed therapy, vasopressors are used to increase MAP so as to maintain CPP as per set goals.

Osmotherapy

If ICP is still elevated, mannitol or hypertonic saline can be started. Mannitol is an osmotic diuretic and also decreases blood viscosity and hematocrit and increases CBF and cerebral oxygen delivery. Use an initial bolus of 0.25–1 g/kg (the higher dose for more urgent reduction of ICP) followed by 0.25–0.5 g/kg boluses repeated every

Flow chart 1 Treatment of raised intracranial pressure
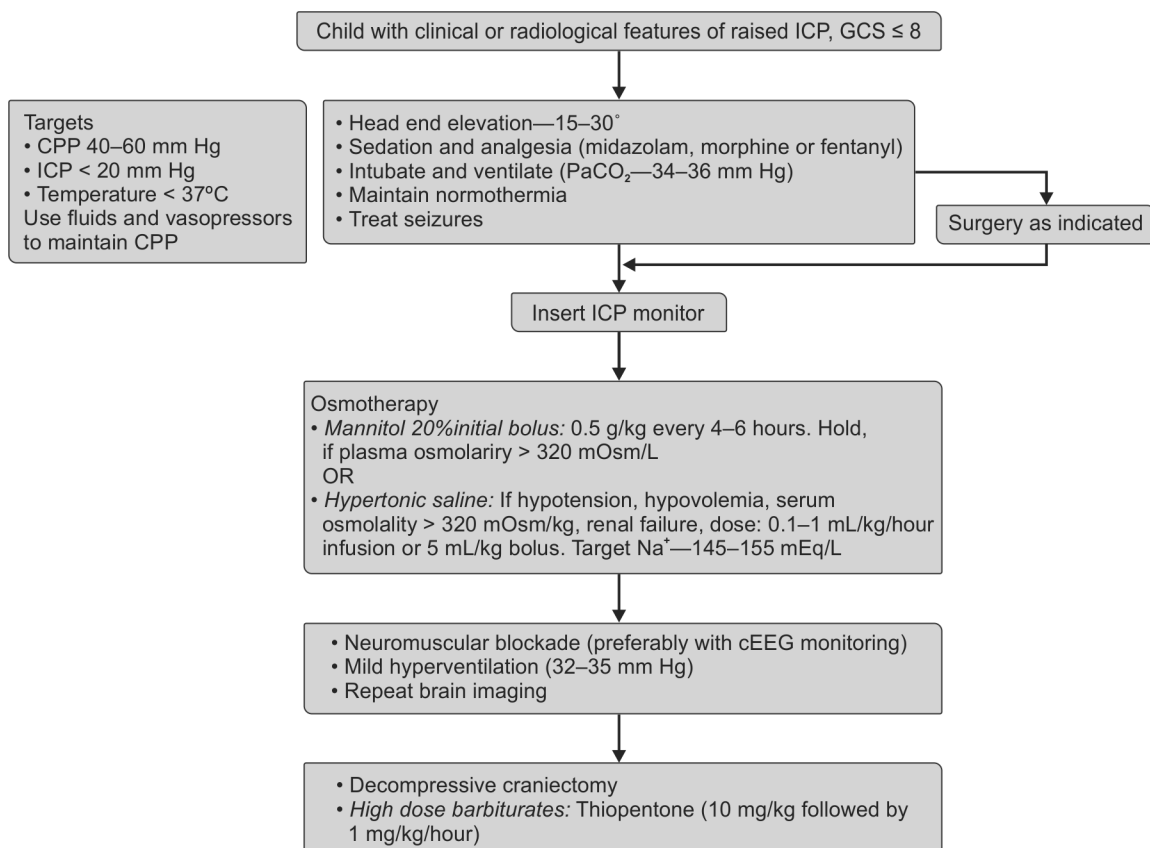
2–6 hours as per requirement. Its duration of effect is 3–5 hours. Hypertonic saline has a clear advantage over mannitol in children who are hypovolemic or hypotensive. Other situations where it may be preferred are renal failure or serum osmolality greater than 320 mOsmol/kg. It has been found effective in patients with serum osmolality of up to 360 mOsmol/kg. It would be reasonable to administer hypertonic saline as a continuous infusion at 0.1–1.0 mL/kg/hour to target a serum sodium level of 145–155 mEq/L.

Hyperventilation

If despite these measures the ICP remains above 20 mm Hg, the ventilator rate can be adjusted to keep PCO_2 30–35 mm Hg. Hyperventilation acts by constriction of cerebral blood vessels and lowering of CBF. However, studies in children with traumatic brain injury have demonstrated aggressive hyperventilation dramatically decreases the CBF, causing or aggravating cerebral ischemia. This often results in poorer outcome in these patients. The most effective use of hyperventilation is for acute, sharp increases in ICP or signs of impending herniation.

Decompressive Craniectomy

This may be considered if above measures fail to control ICP in salvageable patients. Pediatric guidelines of severe TBI suggest the use of decompressive craniectomy as an option in the treatment of medically refractory intracranial hypertension was recommended. The recommendation noted that children with a potentially recoverable brain injury and those who experience secondary deterioration within 48 hours after injury may be more likely to benefit from surgery and that children with severe secondary injury at the time of presentation may be less likely to benefit.

Barbiturate Coma

Pentobarbital can be used to induce burst suppression and control ICP by reducing metabolic activity. A commonly used protocol is to use loading dose of 10 mg/kg over 30 min followed by 1 mg/kg/hour. The complication rate of barbiturate therapy is high and includes hypotension, hypokalemia, respiratory complications, infections, hepatic dysfunction and renal dysfunction.

Hypothermia

Evidence from carefully conducted studies in adults and children do not show any improvement in the neurologic outcome in head injured patients with the use of therapeutic hypothermia. However, studies do suggest a lowered ICP during the hypothermia therapy in children. So in children with refractory raised ICP controlled hypothermia may be tried.

BRAIN DEATH

Brain death is the irreversible cessation of all functions of the entire brain, including the brainstem. Determination of brain death by neurological criteria is a clinical diagnosis. The guidelines for the determination of brain death in children were published by a multi-society task force in the USA in 1987. As per these guidelines, after certain prerequisites are met, the three key components of clinical brain death diagnosis are demonstrations of irreversible coma/unresponsiveness, absence of brainstem reflexes, and apnea. In addition, age-related observation periods and the need for specific ancillary tests were recommended for all children younger than 1 year of age. These guidelines were extensively updated and revised in 2011 **(Table 7)**.

Determination of brain death in neonates, infants and children relies on a clinical diagnosis that is based on the absence of neurologic function with a known irreversible cause of coma. Coma and apnea must coexist to diagnose brain death. This diagnosis should be made by physicians who have evaluated the history and completed the neurologic examinations.

Prerequisites for Initiating Clinical Brain Death Evaluation

Factors potentially influencing the neurologic examination such as dyselectrolytemia, shock and hypothermia (maintain core body temperature > 35°C) must be corrected prior to examination. All sedation, neuromuscular blockers and anticonvulsants must be discontinued for a reasonable time period (based on elimination $t_{1/2}$). The neurological evaluation should be deferred for 24–48 hours after cardiopulmonary resuscitation.

Number of Examinations and Observation Period

Two examinations including apnea testing with each examination separated by an observation period are required. The examinations should be performed by different attending physicians involved in the care of the child. The recommended observation periods are 24 hours for neonates (37 weeks' gestation to term infants 30 days of age) and 12 hours for infants and children (> 30 days to 18 years).

Table 7 Neurological examination components to assess brain death

• *Coma*: Complete loss of consciousness, vocalization, volitional activity, eye opening or eye movements	Noxious stimuli should not produce a motor response other than spinally mediated reflexes
• *Loss of all brainstem reflexes including*	
Midposition or fully dilated pupils which do not respond to light	Usually the pupils are fixed in a midsize or dilated position (4–9 mm)
Absence of movement of bulbar musculature including facial and oropharyngeal muscles	Deep pressure on the condyles at the level of the temporomandibular joints supraorbital ridge should produce no grimacing or facial muscle movement
Absent gag, cough, sucking, and rooting reflex	Tested by stimulating posterior pharynx with a tongue blade and by examining the cough response to tracheal suctioning
Absent corneal reflexes	Absence of eyelid movement by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water
Absent oculovestibular reflexes	The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing)
• Apnea testing	
• Flaccid tone and absence of spontaneous or induced movements, excluding spinal cord events such as reflex withdrawal or spinal myoclonus	Observe the patient for any spontaneous or induced movements. If abnormal movements are present, clinical assessment to determine whether or not these are spinal cord reflexes should be done

Apnea Testing

The patient must have the complete absence of documented respiratory effort (if feasible) by formal apnea testing demonstrating a $PaCO_2$ greater than or equal to 60 mm Hg and greater than or equal to 20 mm Hg increase above baseline. The patient should be preoxygenated using 100% oxygen for 5–10 minutes prior to initiating this test. Mechanical ventilation should be discontinued once the patient is well oxygenated and a normal $PaCO_2$ has been achieved. Follow-up blood gases should be obtained to monitor the rise in $PaCO_2$ while the patient remains disconnected from mechanical ventilation. If no respiratory effort is observed from the initiation of the apnea test to the time the measured $PaCO_2$ greater than or equal to 60 mm Hg and greater than or equal to 20 mm Hg above the baseline level, the apnea test is consistent with brain death. Apnea test should be terminated if oxygen saturations fall below 85% or there is hemodynamic instability.

Ancillary Studies

Ancillary studies (EEG and radionuclide cerebral blood flow) are not required to establish brain death unless the clinical examination or apnea test cannot be completed. These are required:

- To reduce the observation period
- If apnea testing cannot be completed safely due to the underlying medical condition of the patient
- If there is uncertainty about the results of the neurological examination
- If a medication effect may interfere with evaluation of the patient.

If the ancillary study is equivocal or if there is concern about the validity of the ancillary study, the patient cannot be pronounced dead. The patient should continue to be observed until brain death can be declared on clinical examination criteria and apnea testing, or a follow-up ancillary study can be performed to assist with the determination of brain death. A waiting period of 24 hours is recommended before further clinical reevaluation or repeat ancillary study is performed. Supportive patient care should continue during this time period.

Declaration of Brain Death

Brain death is declared after the second neurologic examination and apnea test confirm an unchanged and irreversible condition. When ancillary studies are used, documentation of components from the second clinical examination that can be completed, including a second apnea test, must remain consistent with brain death. All aspects of the clinical examination, including the apnea test, or ancillary studies must be appropriately documented.

IN A NUTSHELL

1. The most common etiology of coma in children are infections (encephalitis, meningitis)
2. Securing cervical spine (in suspected or proven trauma) and stabilization of airway, breathing and circulation is the first step in managing comatose child.
3. The key elements of neurological examination in a comatose child are: level of consciousness, respiratory pattern, brainstem responses (pupillary, corneal reflex, extraocular movements) and motor response.
4. It is important to recognize herniation syndromes and institute immediate therapy to reduce intracranial hypertension.
5. ICP monitoring (intraventricular or parenchymal) helps to decide treatment threshold in comatose child. Its role in traumatic brain injury is well established.
6. The goals of managing raised ICP are to maintain CPP 40–60 mm Hg and keep ICP less than 20 mm Hg.
7. The first tier treatments in raised ICP include intubation, sedation and analgesia, neuromuscular blockade, osmo-therapy and mild hyperventilation.
8. Second tier therapies include aggressive hyperventilation, decompressive craniectomy, barbiturate coma and therapeutic hypothermia.
9. The three key components of clinical brain death diagnosis are demonstrations of irreversible coma/unresponsiveness, absence of brainstem reflexes, and absence of documented respiratory effort by formal apnea test.

MORE ON THIS TOPIC

Edlow JA, Rabinstein A, Traub SJ, Wijdicks EF. Diagnosis of reversible causes of coma. Lancet. 2014.

Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents-second edition. Pediatr Crit Care Med. 2012;13 Suppl 1:S1-82.

Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Crit Care Med. 2011;39:2139-55.

Seshia SS, Bingham WT, Kirkham FJ, Sadanand V. Nontraumatic coma in children and adolescents: diagnosis and management. Neurol Clin. 2011;29:1007-43.

Seshia SS, Bingham WT, Griebel RW. Coma in childhood. Handb Clin Neurol. 2008;90:329-50.

Sharma S, Kochar GS, Sankhyan N, Gulati S. Approach to the child with coma. Indian J Pediatr. 2010;77:1279-87.

Chapter 42.14
Stroke
Ramesh Konanki

Stroke is defined by the World Health Organization (WHO) as *a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting more than 24 hours or leading to death with no obvious nonvascular cause*. The duration cut-off of 24 hours is in the context of defining another vascular event, i.e., transient ischemic attack (TIA) as *a sudden, focal neurologic deficit that lasts for less than 24 hours, of presumed vascular origin, confined to an area of the brain or eye perfused by a specific artery*. More recently the time cut-off has been restricted to less than 1 hour. But, a more pathophysiologically distinctive definition encompasses tissue criteria, i.e., presence or absence of tissue infarction to differentiate stroke (with tissue infarction) vs TIA (no tissue infarction).

Stroke is broadly classified into two types based on primary pathophysiology of disease: *ischemic stroke* due to interruption of blood flow to a part of brain, and *hemorrhagic stroke* due to rupture of blood vessels with bleeding into the cerebral parenchyma. About 55% of pediatric strokes are ischemic in nature and 45% are hemorrhagic strokes. This is in contrast to stroke in adults where 80–85% of the strokes are ischemic and 15–20% hemorrhagic. The ischemic stroke may further be classified into *arterial ischemic stroke* (AIS) due to occlusion of arteries, and *cerebral venous sinus thrombosis* (CVST) resulting from occlusion of venous sinuses **(Figs 1 and 2)**. The objective of this chapter is to highlight the salient features of childhood stroke in terms of classification, etiopathogenesis, clinical presentation and management including optimal evaluation.

ARTERIAL ISCHEMIC STROKE

Epidemiology
The term *childhood stroke* refers to stroke in children aged between 1 month and 18 years. It is not uncommon, with incidence varying depending on the age and geographic location. The reported incidence ranges from 1.2 cases per 100,000 children to 13 cases per 100,000 children (< 18 years of age). The data from International pediatric stroke study shows significant male predominance for childhood ischemic stroke regardless of age or stroke subtype. The age distribution of stroke is highly variable during childhood, disproportionately affecting infants (2.5 per 100,000 children per year) especially those with congenital heart disease and perinatal asphyxia. The stroke incidence decreases to nearly half (1.25 cases per 100,000 children per year) if infants are excluded from the study population. There is no population based data regarding true burden of childhood stroke in India. As per hospital based studies, childhood stroke (1–16 years of age) constitute 5–15% of all strokes in the young (< 40 years) and 0.7% of all pediatric admissions.

Recurrence is estimated to occur in 20% of children with stroke. However, risk factors predicting the recurrence are poorly understood. Stroke recurrence is thought to be more prevalent if multiple risk factors are present.

Etiology
Identification of an etiology in childhood stroke is challenging because of diverse risk factor profile **(Box 1)**. The predominant causes for ischemic stroke in children can be grouped into (1) structural heart disease, (2) vasculopathies (inflammatory and noninflammatory), (3) hematological disorders, and (4) prothrombotic states (inherited and acquired). The prevalence of risk factors varies depending on the geographic location. For example, moyamoya disease is one of the most common causes in Japan, where as sickle cell disease is an important cause in regions with high prevalence of this disease.

Structural Heart Disease and Thromboembolism
Cardiac causes of stroke are more prevalent in younger children (up to 2 years of age). Congenital heart disease, rheumatic heart disease, infective endocarditis and cardiomyopathy are the major cardiac causes of stroke with thromboembolism being the main pathophysiological mechanism. Embolic stroke is an important complication of cardiac surgery during intraoperative and immediate postoperative periods (e.g., Fontan operation).

Another important group of conditions with thromboembolic stroke include trauma to carotid vessels in the neck or throat (anterior circulation stroke), and vertebral artery dissection associated with craniovertebral junction anomalies (posterior circulation stroke).
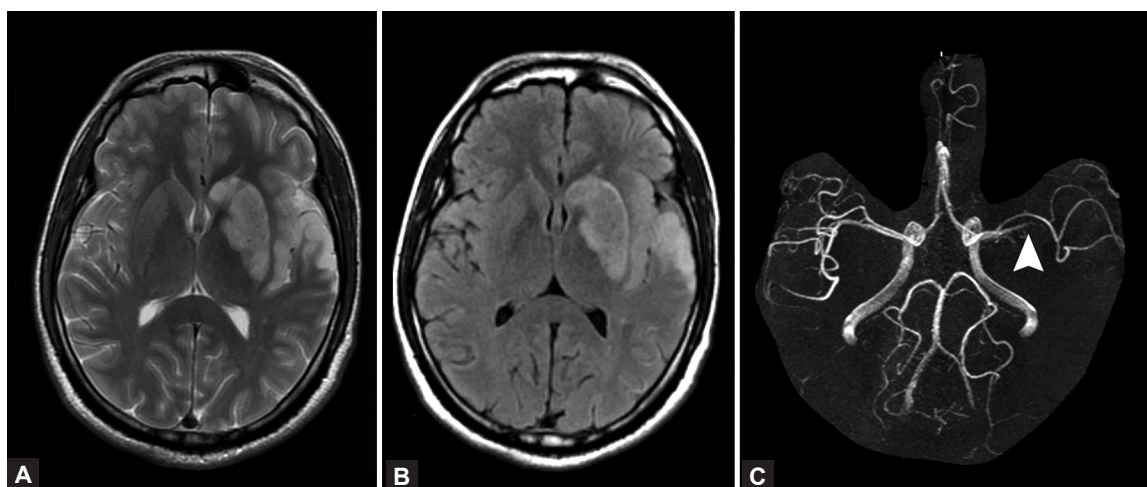
Figures 1A to C Arterial ischemic stroke. (A) Axial T2 and (B) FLAIR images of the brain showing a subacute infarct involving the left temporal lobe, insular cortex, left lentiform and caudate nuclei. (C) MR Angiogram shows early bifurcation of the left middle cerebral artery and occlusion of its inferior division (arrowhead)
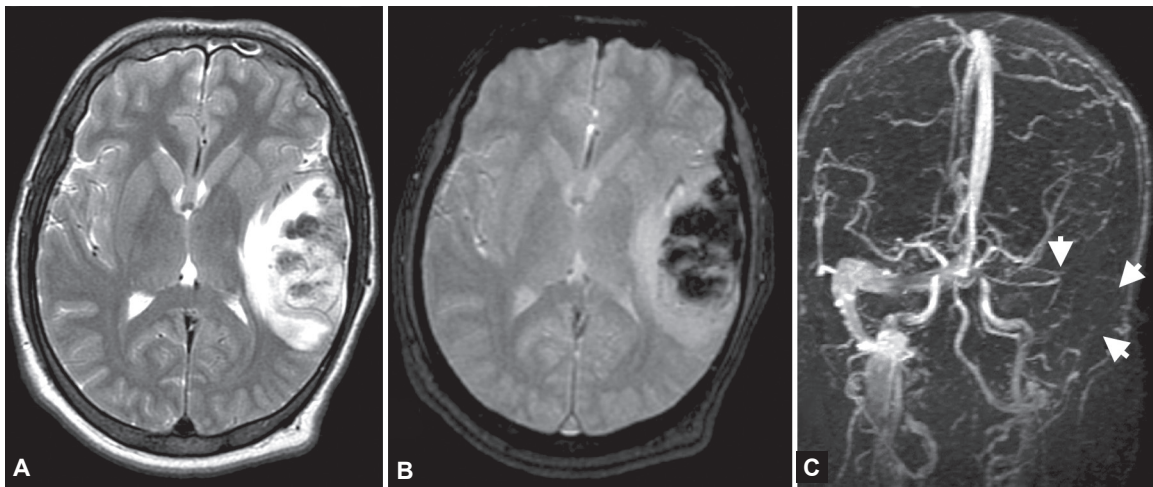
Figures 2A to C Cerebral venous sinus thrombosis. (A) Axial T2 and (B) Gradient recalled echo (GRE) images of the brain showing a venous infarct involving the lateral aspect of the left temporal lobe and temporoparietal region. (C) MR venogram showing occlusion of the left transverse and sigmoid sinuses (arrowheads)

BOX 1 Etiology of ischemic stroke in children

Structural heart disease and thromboembolism
- Congenital heart disease
- Rheumatic heart disease, infective endocarditis
- Cardiomyopathies, arrhythmias
- Prosthetic, prolapsed valves
- Cardiac interventions (e.g., Fontan operation)
- Neck trauma, and craniovertabral junction anomalies

Vasculopathies
- *Infective vasculitis:* Pyogenic, fungal, tuberculous, AIDS, mycoplasma
- *Noninfective vasculitis:* SLE, polyarteritis nodosa, Takayasu arteritis
- Post varicella angiopathy
- *Noninflammatory vasculopathies:* Moyamoya disease, migraine, Marfan syndrome, Ehlers-Danlos syndrome, fibromuscuar dysplasia

Hematological causes
- *Hemoglobinopathies:* Sickle cell anemia
- Thrombocytosis
- Polycythemia
- Lymphoreticular malignancies

Prothrombotic states
- Protein C, S deficiency, antithrombin III deficiency
- Activated protein C resistance, factor V leiden mutation, prothrombin mutation
- Lupus anticoagulant, aCL, IgG and IgM
- Elevated lipoprotein (a)
- Hyperhomocysteinemia and MTHFR mutation

Metabolic causes
- Homocystinuria
- MELAS and Leigh disease
- Fabry disease, Ornithine transcarbamylase deficiency, sulphite oxidase deficiency
- Organic acidemias (Methylmalonic academia, Propionic academia, Isovaleric academia, Glutaric academia type I)

Drugs
- Cocaine, amphetamine, triptans, ergots

Miscellaneous risk factors
- Iron deficiency anemia, lenticulostriate artery mineralization

Abbreviations: SLE, systemic lupus erythematosus; MTHFR, methylenetetrahydrofolate reductase; MELAS mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; aCL, anticardiolipin antibody.

Hematological Causes

Sickle cell disease, thrombocytosis and polycythemia are the second most common etiologies causing ischemic stroke. Children with sickle cell disease are highly vulnerable to cerebrovascular events, with incidence of stroke being as high as 285 cases per 100,000 children. Twenty five percent of patients with sickle cell anemia develop cerebrovascular complications, of which 80% are under 15 years of age. Mean age of stroke is 7.7 years and recurrence risk is 67%.

Vasculopathies

Infective vasculitis, noninfective inflammatory vasculitis and noninflammatory vasculopathies are other major causes of ischemic stroke **(Box 1)**. Of these, moyamoya disease is highly prevalent in Japan and some East Asian countries, whereas infective vasculitides are mostly seen in developing countries with high rates of central nervous system infections **(Figs 3A to C)**. Moyamoya disease is a vasculopathy with progressive stenosis of supraclinoid portion of internal carotid arteries, with development of extensive collaterals from other vascular territories. The appearance of these collaterals on angiogram is given the name *puff of smoke* **(Figs 4 and 6)**. *Moyamoya disease* is a cerebrovascular disorder of unknown etiology characterized by progressive occlusion of supraclinoid internal carotid arteries and variable occlusion of its branches. When the similar clinical and radiological features are seen in association with conditions including Down syndrome, neurofibromatosis, autoimmune disease, cerebrovascular atherosclerosis, cranial irradiation or cerebral neoplasm, it is called *moyamoya syndrome.* Another important childhood vasculopathy is post-varicella angiopathy (PVA). Stroke can be seen in children after varicella infection with latency period ranging from 2–4 weeks to 12 months. It is more frequently seen in anterior circulation, and the diagnosis is confirmed by corroborative evidence of positive varicella zoster specific antibodies in cerebrospinal fluid.

Prothrombotic States

Prothrombotic states (inherited and acquired) account for 20–50% of children with AIS and 33–99% of children with CVST. Of these, factor V Leiden, hyperhomocysteinemia and methylenetetrahydrofolate reductase (MTHFR) polymorphisms, protein C deficiency, and anticardiolipin antibodies are the most
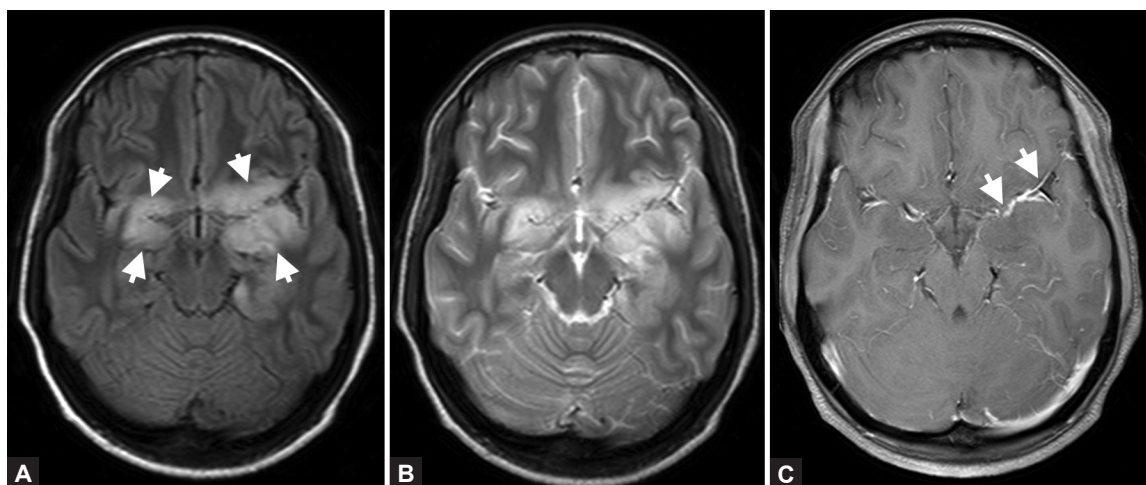
Figures 3A to C Tubercular meningitis with vasculitic infarcts. (A) Axial FLAIR and (B) T2 weighted images of the brain showing nonterritorial infarcts along the margins of the sylvian fissures on either side. (C) Axial postcontrast T1 weighted image shows enhancing exudates within the sylvian fissure (arrowheads)
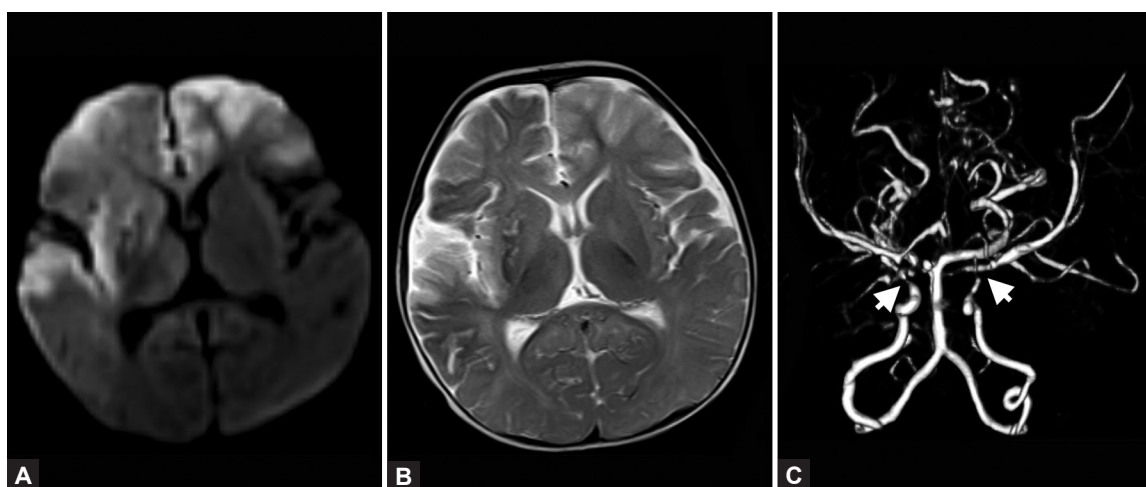
Figures 4A to C Moyamoya disease. (A) Axial diffusion weighted and (B) T2 weighted images of the brain showing subacute infarcts in the distribution of the right middle cerebral and bilateral anterior cerebral arteries. (C) MR angiogram shows critical stenosis involving the terminal segments of both internal carotid arteries (arrowheads)

common inherited prothrombotic states. Acquired prothrombotic states include chronic liver disease and protein-losing states like nephrotic syndrome. The data from hospital-based studies has shown hyperhomocysteinemia, MTHFR polymorphism, protein C and S deficiency and antiphospholipid antibodies as the most common prothrombotic states among Indian children with ischemic stroke.

Metabolic Causes

Homocystinuria, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS), Leigh disease, familial hyperlipidemias, Fabry disease and organic acidemias (methylmalonic aciduria, propionic acidemias, isovaleric acidemias, glutaric acidemia type I) are some of the rare causes of ischemic stroke.

Miscellaneous Risk Factors

Focal cerebral arteriopathy is another vasculopathy affecting lateral lenticulostriate arteries due to vessel wall involvement of distal internal carotid artery or proximal middle or anterior cerebral arteries. It may be progressive (5–10% children) or transient (nearly 90%). Serial neuroimaging is indicated in children suspected with focal cerebral arteriopathy. *Mineralization of lenticulostriate arteries* is another recently described clinic-radiological entity causing subcortical stroke in infants especially following minor injury **(Figs 5A to C)**. Recent reports have also suggested an association between iron deficiency anemia and ischemic stroke, especially in children between 6 months and18 months of age.

Etiology of Posterior Circulation Stroke

Ischemic stroke in posterior circulation (vertebrobasilar arteries and their territories) has slightly different set of causes including vertebral artery dissection following neck trauma, craniovertebral junction anomalies apart from other hematological and prothrombotic states **(Figs 7A to C)**.

Pathophysiology

Thromboembolism is the most common mechanism of stroke with source of thrombus being either the cerebral arteries themselves (vasculitis, vasculopathies, prothrombotic states
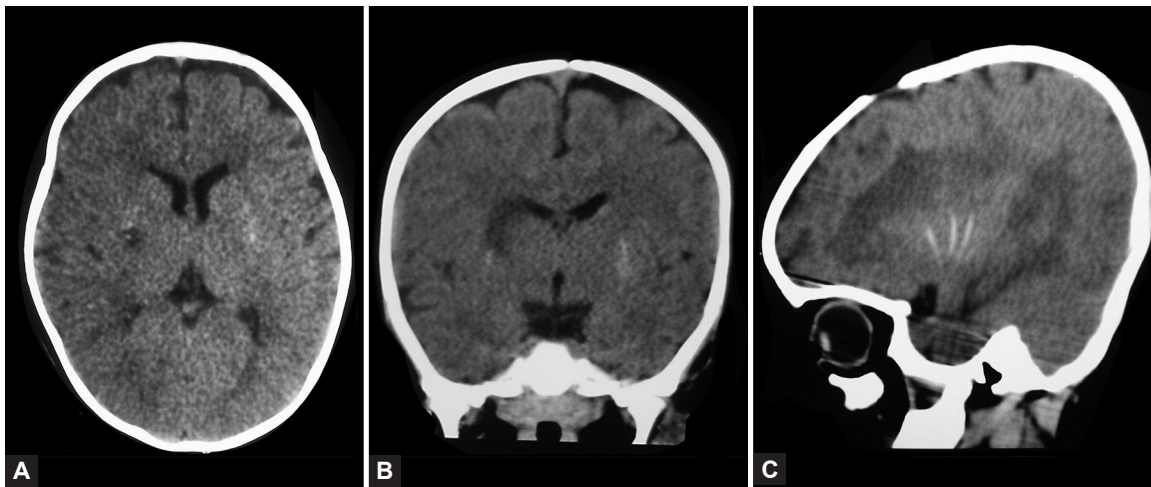
Figures 5A to C Mineralizing angiopathy of lenticulostriate arteries with subcortical stroke in infants. (A) Axial, (B) Coronal and (C) Sagittal reconstructions from a multislice brain CT study of a child with mineralizing angiopathy with stroke. *Note:* (A) the hypodensity in right capsuloganglionic region (infarct) with central dot like hyperdensity (mineralized vessel). (B and C) the linear, vertically oriented mineralization along the course of lenticulostriate arteries within the putamina on either side. (B) Subacute infarct is seen in the right putamen, extending superiorly from the terminal part of one of these mineralized vessels
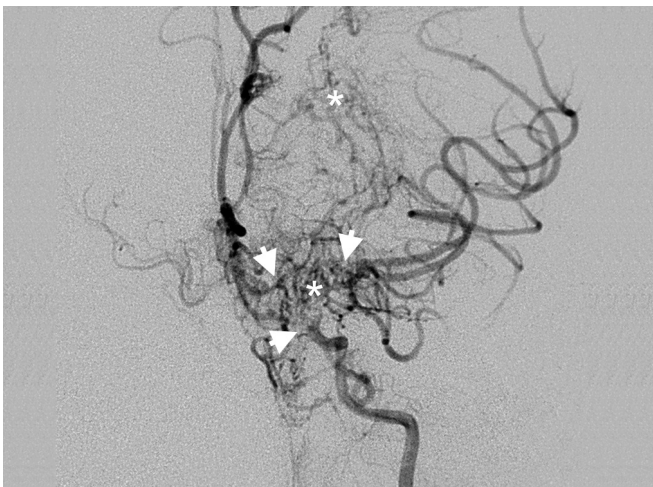
Figure 6 Digital subtraction angiography. Frontal projection of left internal carotid artery injection showing occlusion of the terminal part of internal carotid artery and proximal segments of anterior and middle cerebral arteries (arrowheads). *Moyamoya* collaterals (asterix) are seen, giving a "puff of smoke" appearance

and hematological disorders) or the heart and major vessels (cardioembolism).

The pathophysiology of cerebral ischemia consists of primary and secondary injury. *Primary injury* implies the cellular dysfunction caused directly by ischemic insult. The chain of events and derangements set into motion by the primary injury constitute the *secondary injury*. Prominent in the tissue damage caused by cerebral ischemia is the presence of a *central core*—where ischemia is most severe with rapid development of tissue infarction and neuronal cell death. The area surrounding the central core, which is marginally perfused, is called the *penumbra*. Penumbra has the capacity to recover when perfusion is restored promptly. The balance between cerebral metabolic rate and the supply of oxygen and glucose determines extent of penumbra, and thus the severity of stroke. This has therapeutic implications, in that early restoration of blood flow by thrombolysis may prevent the extent

of neuronal damage, hence, the need for emergent therapies like thrombolysis and other neuroprotective strategies.

Clinical Features

The evolution of symptoms of stroke is often hyperacute to acute in children, i.e., the onset to peak symptoms usually takes hours. This is true especially for embolic strokes. For thrombotic strokes (e.g., following neck trauma and vasculopathies) one may see less abrupt onset or stuttering course, determined by the rapidity of thrombus formation and occlusion or embolization distally. The severity of symptoms is often maximum at onset with gradual improvement thereafter.

The presenting symptoms depend on the anatomical and functional areas of brain affected, and often give clues to likely etiology **(Table 1)**. The common symptomatology includes one or more focal neurological deficits, i.e., hemiparesis (most common presentation), dysarthria, aphasia, gaze palsies, facial nerve palsy, hemianopsia and diplopia. Many children, especially infants and young children, also manifest nonspecific features like headache, drowsiness, irritability and behavioral abnormalities. Isolated extrapyramidal symptoms like hemidystonia may be presenting symptom in infants with subcortical strokes involving perforating arteries.

Differential Diagnosis

Todd's Palsy

Transient weakness of one or more body parts following seizure in those parts, which lasts variably from 30 minutes to 36 hours. Neuronal exhaustion following continuous firing during seizure is the possible explanation for Todd's palsy. Hemiparesis is the most common manifestation and usually resolves completely without any treatment.

Acute Demyelinating Event

Acute disseminated encephalomyelitis (ADEM) is the most common demyelinating event in childhood. Mono or hemiparesis may be the presenting symptom in many cases, often associated with significant encephalopathy. A preceding febrile illness or recent vaccination is the most common trigger. Neuroimaging, especially magnetic
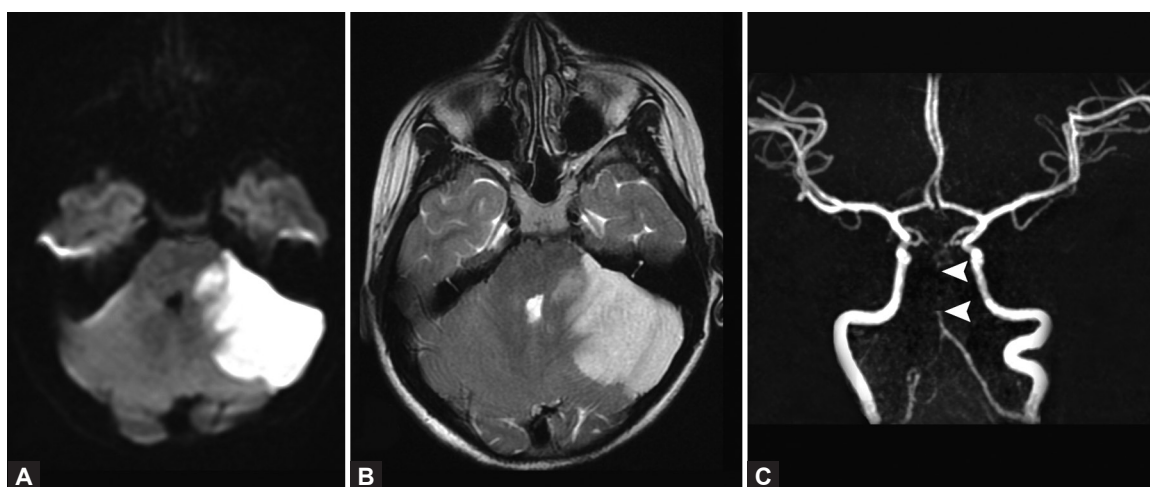
Figures 7A to C Posterior circulation stroke. (A) Axial diffusion weighted and (B) T2 weighted images of the brain showing subacute infarct in the distribution of the left superior cerebellar artery. (C) MR angiogram shows occlusion of the mid and distal thirds of the basilar artery (arrowheads)

Table 1 Salient features: Clues to underlying etiology of stroke

Finding	Likely etiology
History of neck trauma or fall with object in oral cavity	Carotid artery thrombosis with or without dissection, posterior circulation stroke due to vertebral artery dissection
Trivial fall or minor trauma in young children	Lenticulostriate artery mineralization with subcortical stroke
History of blood transfusions	Sickle cell disease
History of recurrent abortions in mother	Anti-phospholipid antibodies (aCL and lupus anticoagulant)
Family history of stroke in young (< 40 years), premature cardiac death, unexplained deep venous thrombosis	Familial hyperlipidemias, inherited prothrombotic states
History of varicella (preceding 6–12 months)	Postvaricella angiopathy
Prior developmental delay	Congenital heart disease and chronic systemic diseases (predominant motor delay), inborn errors of metabolism, mitochondrial cytopathies
Recurrent headaches	Familial hemiplegic migraine, MELAS
Stroke during the course of febrile illness, with encephalopathy	Pyogenic or tubercular meningitis with arteritic infarcts
Antecedent or concurrent respiratory infection	Mycoplasma-associated stroke
Recurrent hemidystonias	Subcortical stroke involving perforating arteries to basal ganglia
Irregular peripheral pulses	Takayasu arteritis
Hypertension (Pre-existent or concurrently developing)	Moyamoya disease (Renovascular hypertension), TTP, SLE
Moderate-severe anemia	Sickle cell disease, iron deficiency anemia, chronic systemic disease
Cardiac murmur	Congenital heart disease, rheumatic heart disease
Facial dysmorphism	Down syndrome (Associated with Moyamoya syndrome and posterior circulation stroke)
Multiple café-au-lait macules	Neurofibromatosis (Associated with Moyamoya syndrome)
Lens dislocation	Homocystinuria, Sulfite oxidase deficiency, Marfan syndrome
Skin rash	SLE, Fabry disease (Angiokeratomas), TTP, Lymphoreticular malignancies
Recurrent strokes	Moyamoya disease, inherited prothrombotic states, metabolic stroke, sickle cell disease, major structural heart disease

Abbreviations: MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

resonance imaging (MRI) confirms the nonvascular demyelinating nature of the disorder with predominant involvement of white matter, with or without gray matter involvement.

Strokelike Episodes in MELAS
The focal neurological deficits of acute onset may be seen in this condition. They may be transient or may persist for prolonged periods ranging from days to months. They are attributed to thrombus formation secondary to cellular energy failure in the vascular endothelium. Hence, the infarcts on neuroimaging characteristically do not follow the arterial territories of brain. Elevation of lactate in arterial blood and cerebrospinal fluid (CSF), and lactate peak on magnetic resonance spectroscopy (MRS) suggests this possibility.

Intracranial Space-Occupying Lesions (ICSOL)
Focal symptoms and signs may be a presenting feature of inflammatory granulomas such as neurocysticercosis (NCC) and

tuberculoma, pyogenic brain abscesses, fungal granulomas and brain tumors. Neuroimaging (MRI) helps in differentiating these pathologies.

Posterior Reversible Encephalopathy Syndrome (PRES)

Acute onset encephalopathy with or without neurological deficits in children with acute onset hypertension. It predominantly affects posterior brain regions (parieto-occipital areas)—both gray and white matter, and sometimes brainstem. It usually resolves in days to weeks.

Recurrent Episodic Hemiparesis

Alternating hemiplegia of childhood (AHC) and familial hemiplegic migraine (FHM) are the channelopathies with recurrent episodic weakness. The FHM is an autosomal dominant form of migraine with aura resulting from mutations in calcium ion channel (CACNL1A4). The AHC is another autosomal dominant channelopathy (ATP1A2 mutations) manifesting as recurrent flaccid hemiparesis, often alternating between the sides. Neuroimaging is normal in these conditions, and genetic testing confirms the diagnosis.

Approach to Diagnosis and Evaluation

In children presenting with acute onset neurological deficits, first step is to confirm the vascular nature of pathology, followed by evaluation for possible etiologies and risk factors.

Neuroimaging

Neuroimaging of brain is the cornerstone for arriving at diagnosis of stroke by confirming the vascular nature and ruling out other mimicking conditions. Neuroimaging is indicated as early as possible in children with suspected stroke. The MRI is the most useful imaging modality in ischemic stroke, complemented by magnetic resonance angiography (MRA) and venography (MRV). The computerized tomography (CT) and digital subtraction angio-graphy (DSA) are indicated in specific situations **(Figs 5 and 6)**.

Magnetic Resonance Imaging

The MRI of brain is the gold standard for diagnosis of stroke. It typically includes T1W, T2W, T2-FLAIR and diffusion weighted imaging (DWI) sequences. The DWI is the most sensitive MRI sequence to identify early and small ischemic infarcts in AIS **(Figs 4A and 7A)**. The DWI can pick up abnormalities as early as 4–6 hours. Hence, DWI should always be included in children with suspected stroke. All children with ischemic stroke should also be evaluated with MRA to assess patency of cerebral vessels as well as neck vessels (including carotid arteries and vertebrobasilar system).

Computerized Tomography (CT)

The CT of brain has limited role in evaluation of children with ischemic stroke. One indication for CT in child with suspected stroke is in the setting of significant hemodynamic instability or encephalopathy making the sedation and transport of the child difficult. In emergency situations, CT also helps in ruling out hemorrhagic stroke.

In the recently described entity of lenticulostriate artery mineralization in infants with subcortical stroke, CT is the pre-ferred imaging modality. This condition is suspected when children between 6 months and 24 months present with acute hemiparesis and hemidystonia following trivial fall or minor trauma. While axial CT sections show only hyperdense dots with surrounding hypodensity in the region of basal ganglia, the sagittal

and coronal reconstructed sections clearly demonstrate the linear mineralization of these perforating arteries (linear hyperdensities along vessels) along with infarct (hypodensity) **(Figs 5A to C)**.

Digital Subtraction Angiography (DSA)

It is the gold standard for diagnosis of vasculopathies, hence is performed in children with suspected moyamoya disease, small vessel vasculitis, cervicocephalic arterial dissection and arterial stenosis of other etiologies **(Fig. 6)**.

Transcranial Doppler (TCD)

The transcranial Doppler is a noninvasive test to measure blood flow velocity in major cerebral vessels. It has been well studies in children with sickle cell disease (SCD), to monitor the stroke risk and deciding the need for blood transfusion. Typically, children with time-averaged mean velocity of more than 200 cm/s on TCD have higher risk of stroke. Hence, it is recommended that in children with SCD, periodic TCD should be done: annually if initial TCD is normal, a month later if abnormal, and 3–6 months later if borderline abnormal.

Etiological Evaluation

A thorough clinical evaluation including prior neurodevelopmental status, 3-generation family history, detailed physical and neurological examination, and focused examination of cardiovascular system (especially cardiac murmurs, carotid bruit, peripheral pulses and blood pressure in all four limbs) should be done in all children. The salient clues on history and physical examination are given in **Table 1**.

The risk factors for childhood stroke are multiple and evaluation should be individualized based on the age, family history, type of stroke (AIS or CVST), geographic location and comorbidities, e.g., sickle cell disease, congenital heart disease, head and neck trauma, etc. The necessary investigations are given in **Table 2**. The initial universal investigations (Level 1) are aimed to evaluate for most common causes and treatable causes of ischemic stroke, hence, mandatory in all children. Evaluation of inherited prothrombotic states is desirable in all children with ischemic stroke, but, the necessary investigations from this list may be individualized (Level 2). For example, protein C deficiency, protein S deficiency, antithrombin deficiency, elevated lipoprotein (a), and mutations of factor V Leiden and prothrombin genes are seen with both AIS and CVST, whereas MTHFR polymorphisms and antiphospholipid antibodies are mainly associated with AIS. The Level 3 investigations are indicated in selected children as these are rare causes (Inborn errors of metabolism, collagen vascular disorders and mitochondrial cytopathies) or restricted to certain geographic locations (e.g., Hb-electrophoresis). The prothrombotic investigations like protein C deficiency, protein S deficiency, antithrombin deficiency, elevated lipoprotein (a) should be preferably done at least 3 months after the acute stroke event, to reduce the possibility of falsely low levels of anticoagulant proteins.

MANAGEMENT OF ARTERIAL ISCHEMIC STORKE

Stabilization and Supportive Care

Stroke in children is a neurological emergency and requires multidisciplinary care involving pediatric neurologist, intensivist and the nursing staff. Similar to any medical emergency, the initial part of management includes stabilization of vital functions and supportive care for associated complications and comorbidities. The overview of management of childhood ischemic stroke is given in **Flow chart 1**.

Table 2 Investigations for children with ischemic stroke

Level 1: Mandatory in all children	
Complete blood counts including platelet count and RBC indices, erythrocyte sedimentation rate, C-reactive protein, peripheral smear for RBCs and atypical cells, sickle cell screening, fasting lipid profile, 2D-echocardiogram, ECG, carotid Doppler, liver function tests and renal function tests, serum iron studies	
Level 2: Preferable to do in all children, may be individualized	
Protein C, Protein S, Anti-thrombin III, APCR, Factor V Leiden, plasma homocysteine, anticardiolipin antibodies (aCL-IgM, IgG), Lupus anticoagulant, lipoprotein (a), MTHFR polymorphisms, Prothrombin gene mutations	
Level 3: Indicated in selected children	
Preceding respiratory infection	Mycoplasma serology
Collagen vascular diseases (Chronic systemic features like pyrexia, weight loss, joint pains, lymphadenopathy, cytopenias)	ANA, Anti-ds DNA
Mitochondrial cytopathies (Failure to thrive, recurrent strokes/stroke-like episodes, short stature, respiratory irregularities, myoclonic epilepsy)	Arterial lactate, CSF lactate, muscle biopsy, mitochondrial mutations
Inborn errors of metabolism (consanguinity, siblings affected/died, episodic symptoms)	Ammonia, arterial lactate, blood-TMS, urinary organic acids by GC-MS
Sickle cell disease (Endemic area for sickle cell disease, past history of blood transfusions, severe anemia, hemolytic facies)	Hb-electrophoresis
Failure to thrive, hepatosplenomegaly, recurrent infections	Mantoux test, chest X-ray, retroviral serology
Adolescents with suspected use of illicit drugs	Toxicology screen of blood and urine

Abbreviations: ANA, anti-nuclear antibodies; APCR, activated protein C resistance; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; ECG, electrocardiogram; GC-MS, gas chromatography-mass spectrometry; MTHFR, methylenetetrahydrofolate reductase; RBC, red blood cells; TMS, tandem mass spectrometry.

The care of airway, breathing and circulation is of prime importance. The oxygen saturation (SpO_2) should be maintained more than 90% with the use of supplemental oxygen, and if necessary, mechanical ventilation. Aggressive treatment of fever, systemic hypertension, hypoglycemia and hypovolemia should be done (as per standard protocols) as they help in maintaining adequate cerebral perfusion and meet cerebral energy requirements. In children with sickle cell disease and stroke, adequate hydration and exchange transfusion to keep HbS more than 30% is the mainstay of treatment. The neurological complications like seizures and raised intracranial pressure should also be managed aggressively. This will help further in limiting the cerebral neuronal injury caused by ischemia. The raised intracranial pressure may be treated using either mannitol or hypertonic saline (3% saline) in the acute phase and hyperventilation for shorter periods. Rarely, emergent decompressive craniectomy may be needed in cases with malignant cerebral edema not responding to medical measures and with impending risk of herniation. There is no evidence to suggest beneficial effect of hypothermia in children with stroke. There is no role of prophylactic anticonvulsants in the absence of clinical or electrographic seizures.

Thrombolytic Therapy

So far, there is no conclusive evidence to suggest the safety and efficacy of thrombolytic therapy (tPA: tissue plasminogen activator) in children with ischemic stroke.

Anticoagulant Therapy

Acute Phase Anticoagulation

Most of the available guidelines suggest use of anticoagulation agents (Unfractionated heparin or low molecular weight heparin, i.e., LMWH) for anticoagulation in the acute phase in conditions which might benefit substantially. For example, carotid artery or vertebral artery dissection, structural heart disease, vasculopathies like carotid/vertebral artery dissection, and suspected inherited prothrombotic states where the risk of propagating thrombus or recurrence risk is considered to be higher. It is usually continued till the evaluation for etiology of stroke is completed. The LMWH has several advantages: fewer side effects and drug interactions, less need for monitoring, and easy to administer (subcutaneous route).

Long-term Anticoagulation

Based on the information on etiology and risk factors in an individual child, the risks and benefits of long-term anticoagulation (3–12 months or more) are assessed. It is recommended for children with substantial risk of recurrent stroke. The anticoagulants are safe and effective for secondary prevention of ischemic stroke in children. After the neonatal period, anticoagulant therapy is recommended for stroke prevention in children. The indications for long-term use of anticoagulants include major structural heart disease with risk of recurrent cardio embolism (to be continued till repair of defect), carotid artery dissection, and inherited prothrombotic states. The options include LMWH and Warfarin. When initiating warfarin, both heparin and warfarin are used together with overlap of few days till INR of 2.0–3.0 is reached, and the heparin is then discontinued. The schedule and doses of anticoagulants and antiplatelet drugs are given in **Table 3**.

Antiplatelet Drugs

In children who are not on anticoagulants, aspirin or clopidogrel are reasonable choices for secondary prevention of recurrent stroke for a period of 12–60 months. These are indicated in children who are assessed to have a lower risk of recurrent embolism or prothrombotic states **(Table 3)**. In children who are advised long-term aspirin therapy, varicella vaccination and annual influenza vaccination is recommended to reduce the risk of Reye syndrome.

Surgical Management

Revascularization surgeries (direct and indirect techniques) are recommended as the first line measure for preventing recurrent strokes in moyamoya disease/syndrome. Emergency decompressive craniectomy may be considered in children with ischemic stroke and malignant cerebral edema (impending herniation) or posterior circulation stroke compromising the brainstem functioning. This may be helpful only if done in the earliest stages before permanent brainstem dysfunction occur. The likely benefits of reducing intracranial pressure should be weighed against the possibility of long-term neurological morbidity (vegetative state) of the survivors.

Rehabilitation and Chronic Management

The rehabilitation is initiated during the acute period (whenever child is hemodynamically and neurologically stable) and

Flow chart 1 Overview of management of ischemic stroke in children
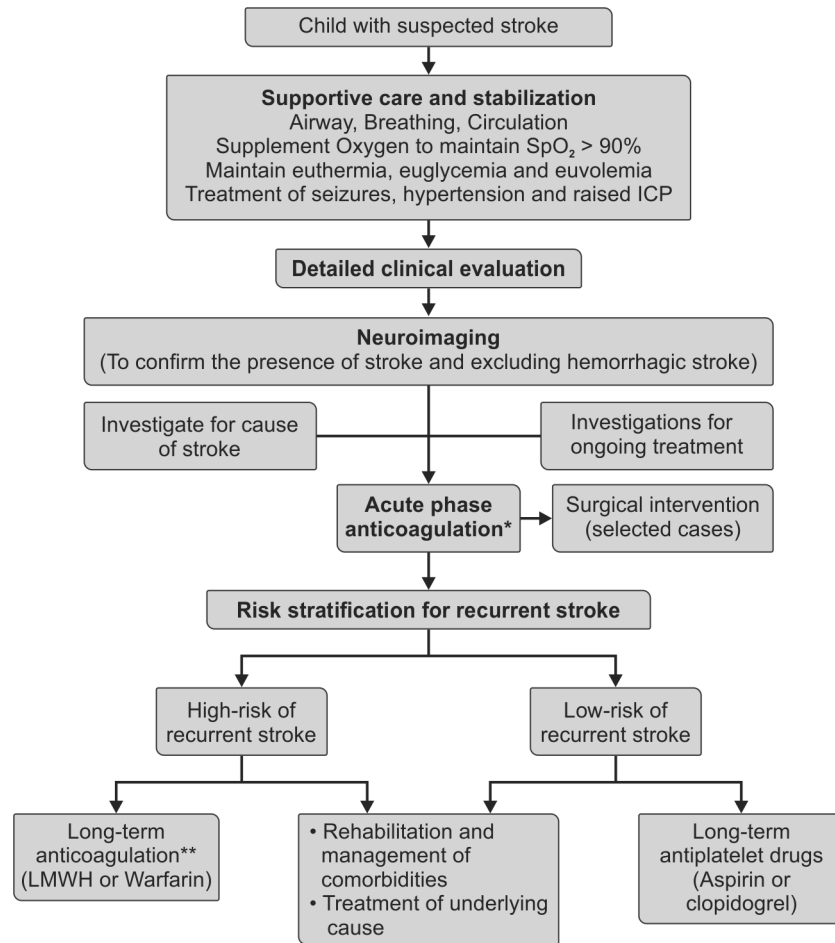
* Acute phase anticoagulation can be considered in all children with AIS and CVST pending etiological investigations. It is definitely indicated in those with carotid artery dissection, complex structural heart disease and propagating thrombus of any cause
** For a variable duration ranging between 3 months and 12 months or longer depending on the persistence of recurrence risk

Table 3 Dosages of medications in ischemic stroke

Drug	Dose
LMWH: Enoxaparin	*Infants < 2 months:* 1.5 mg/kg/dose; subcutaneous; 12 hourly *Children > 2 months:* 1.0 mg/kg/dose; subcutaneous; 12 hourly (Half of the above doses are used as prophylactic dose)
LMWH: Dalteparin	*All age groups:* 150 U/kg/day; subcutaneous
Unfractionated heparin	*Loading:* 75 U/kg IV over 10 minutes *Maintenance:* 28 U/kg/h (Infants < 1 year); 20 U/kg/hour (> 1 year) Titrate dose to maintain target aPTT between 60 and 85

Warfarin	Day 1: 0.2 mg/kg/day single dose
	Day 2–4: Titrated based on INR (Target > 3.5)
	  1–1.4: Repeat day 1 dose
	  1.5–3.0: Increase by 50%
	  3.1–3.5: Increase by 25%
	> 5th day: Target INR: 2–3
	  1.1–1.4: Increase by 20%
	  1.5–2.0: Increase by 10%

Aspirin	3–5 mg/kg/day as single dose; Oral
Clopidogrel	1 mg/kg/day; Oral

Abbreviation: LMWH, low molecular weight heparin.

continued during the follow-up period till optimum functional status is reached. The team includes physiotherapy (strengthening of weak muscles, stretching of spastic muscles, gait training, oromotor stimulation to improve swallowing, etc.), occupational therapy (helping for activities of daily living, feeding and hand function), child psychologist (treatment of behavioral problems and family counseling), speech therapist, and use of orthoses and other assistive devices where needed. Newer rehabilitation techniques like modified constraint-induced movement therapy (CIMT) is useful for children with hemiparesis. The transcranial magnetic stimulation (TMS) is another technique often being used in rehabilitation of adults with stroke. Its utility is still being researched in pediatric stroke rehabilitation.

The long-term management also includes treatment of comorbidities like epilepsy, learning difficulties, dysarthria, behavioral problems like hyperactivity, inattention, aggressive behavior, etc.

Prognosis

Stroke in children entails significant long-term neurological morbidity and mortality (5–20%). The common neuropsychomotor impairments includes motor developmental delay, gait disturbances, epilepsy, learning difficulties, feeding and swallowing difficulties, drooling and scholastic difficulties from various factors. The severity and multiplicity of these morbidities is related

to the underlying cause and risk factors as well as the extent of cerebral neuronal damage. The factors predicting poor outcomes include presence of multiple risk factors, involvement of cerebral cortex, associated systemic illness, large size of infarct, and moyamoya disease.

The recurrence rate of ischemic stroke in children is 10–25% with associated higher risk of mortality. The recurrence risk is higher in children with multiple co-existing risk factors. Hence, it is advisable to evaluate for all risk factors even when one risk factor is identified on initial investigations.

CEREBRAL VENOUS SINUS THROMBOSIS

The clinical presentation often include nonspecific features like altered sensorium, seizures, headache, intracranial hemorrhages (subdural, subarachnoid or intraparenchymal), hydrocephalus, and pseudotumor cerebri. Pathophysiologically, the CVST also results in events similar to arterial occlusion. Since venous occlusion results in increased venous pressure, there is a tendency for blood vessels to rupture producing secondary hemorrhage. This may also cause a marked increase in intracranial pressure.

Apart from the risk factors associated with AIS, there are unique associations with CVST including dehydration, head and neck infections (mastoiditis, rhinosinusitis, and meningitis), beta thalassemia, drugs like L-asparginase and erythropoietin-alpha, and iron deficiency anemia. The prothrombotic states are found in up to 2/3rd of children with CVST.

MRI with MRV is the preferred imaging modality in children with suspected CVST **(Figs 2A to C)**. Secondary hemorrhages are often seen along with the ischemic infarcts in the draining areas. In the absence of significant hemorrhages, acute phase anticoagulation with unfractionated heparin or LMWH is recommended for CVST in children. The anticoagulation with LMWH or Warfarin is usually continued for 3–6 months, with duration depending on the extent of recanalization of venous sinuses in follow-up.

Apart from monitoring development, these children should be specifically followed-up for ophthalmological sequelae including reduced visual acuity and visual field defects.

HEMORRHAGIC STROKE

The common causes of hemorrhagic stroke other than trauma include vascular malformations (arteriovenous malformations, cavernous malformations, and aneurysms), coagulopathies, thrombocytopenia, brain tumors, and rarely, hypertension **(Figs 8**

and 9). The onset of symptoms is more dramatic and progression much faster in hemorrhagic stroke as compared to ischemic stroke.

The common presenting symptoms includes acute onset severe headache, vomiting and rapid worsening of sensorium due to raised intracranial pressure. The damage caused by intracranial hemorrhage is three folds. First, collection of blood may act as space occupying lesion and can worsen the rise in intracranial pressure. Second, disruption of blood brain barrier also promotes development of cerebral edema. Third, presence of blood and erythrocyte breakdown products may add to the pre-existing damage and can sometime result in hydrocephalus.

Children with nontraumatic hemorrhage should be evaluated to look for cause of hemorrhage including neuroimaging (MRI, MRA and 4-vessel angiography in selected cases), coagulation defects, platelet count, etc.

Management includes initial stabilization and supportive care, correction of coagulation defects and thrombocytopenia if identified. The surgical evacuation of hematoma may be beneficial in children with large posterior fossa hematomas, and large supratentorial hematomas with midline shift and impending herniation. In children with vascular malformations, definitive therapy of malformations is advised in those with higher risk of rebleeding. The therapeutic options include endovascular or

Figure 8 Hemorrhagic stroke. Plain axial CT scan performed one day after the onset of ataxia showing an acute hematoma in the left cerebellar white matter
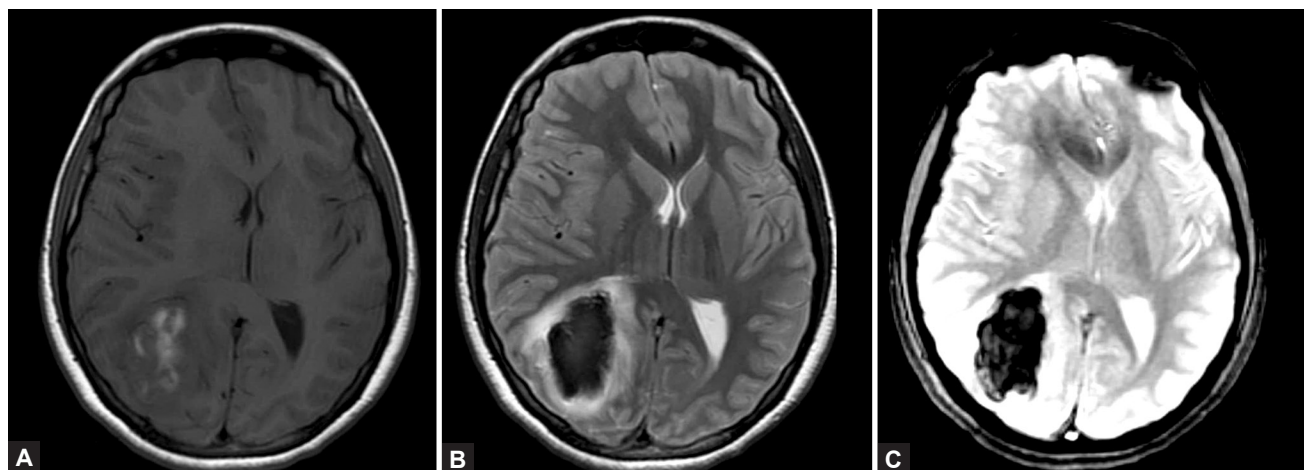
Figures 9A to C MRI in subacute parenchymal hematoma. (A) Axial T1, (B) T2 and (C) Gradient recalled echo (GRE) images of the brain showing a subacute hematoma in the right occipital lobe

surgical obliteration of aneurysms and AV malformations, and radiosurgery (difficult-to-approach malformations).

MORE ON THIS TOPIC

Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G. Male predominance in childhood ischemic stroke: findings from the International pediatric stroke study. Stroke. 2009;40:52-7.

Lingappa L, Varma RD, Siddaiahgari S, Konanki R. Mineralizing angiopathy with infantile basal ganglia stroke after minor trauma. Dev Med Child Neurol. 2014;56:78-84.

Makhija S, Aneja S, Tripathi RP, Narayan S. Etiological profile of stroke and its relation with prothrombotic states. Indian J Pediatr. 2008;75:579-84.

Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: Evidence-Based Clinical Practice Guidelines (8th ed). Chest. 2008;133 (Suppl):887S-968S.

Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: A scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008;39:2644-91.

Thorvaldsen P, Asplund K, Kuulusmaa K, et al. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke. 1995;26:361-7.

IN A NUTSHELL

1. Ischemic stroke is the most common form of stroke in children.
2. The etiology and risk factors for childhood stroke are much more diverse as compared to stroke in adults.
3. Structural heart disease and hematological disorders are the most common causes around the world.
4. Infection is an important risk factor for childhood stroke in developing countries.
5. All attempts should be made to identify as many as risk factors as possible. This helps in secondary prevention.
6. The presenting symptoms may be nonspecific in infants and young children.
7. Arterial dissections, structural heart disease with continued risk of embolism and inherited prothrombotic states are indications for anticoagulation therapy in acute phase (LMWH) as well as long-term (Warfarin).
8. Anti-platelet drugs are the mainstay of secondary prevention for most cases of childhood stroke.
9. Rehabilitation is an essential component of long-term care of children with stroke.

Chapter 42.15
Pyogenic Meningitis
B Talukdar

Pyogenic meningitis is one of the important causes of mortality and cerebral damage in infants and children; 90% of the reported cases occur in children between 1 month and 5 years of age. Relative deficiency in host defense mechanism appears to be the cause of this selective age predilection. In India about a decade back, 1.5% of hospital admissions were due to bacterial meningitis and the case fatality rate was 16%; this probably holds good even today. Globally, the median incidence for acute bacterial meningitis is projected as 34.0 (16.0–88.0) per 100,000 child-years, with a median case-fatality rate of 14.4% (5.3–26.2%) in a recent survey based on 71 studies categorized by 6 World Health Organization regions.

ETIOLOGY

The most common organisms causing pyogenic meningitis in children beyond the neonatal period are similar worldwide and include *Haemophilus influenzae type B*, *Streptococcus pneumoniae* and *Neisseria meningitidis*. About 90% of the cases of pyogenic meningitis are caused by these three bacteria. Of these three organisms, most common is *S. pneumoniae* followed by *H. influenzae* and then *N. meningitidis.* Preventive immunization in early childhood has however changed this pattern in some places; in USA *Haemophilus* has been virtually wiped out and *N. meningitidis* is now the most common pathogen causing pyogenic meningitis.

The most common serotypes of *S. pneumoniae* that cause invasive disease are 4, 6B, 9V, 14, 18C, 19F and 23F. The most common type of *H. influenzae* is type b out of its 6 serotypes. Invasive disease due to *N. meningitides* is caused by the strains of groups A, B, C, Y and W-135; in India most common cause is group A strain, group B strain is rare. Other organisms are *Staphylococcus aureus, E. coli, Klebsiella, Proteus, Acinetobacter, Pseudomonas* and *Salmonella. Staphylococcus* is often seen in association with pyoderma. *Pseudomonas* usually is an opportunistic infection commonly seen in presence of immunocompromised states like malignancy, immunodeficiency disorders, malnutrition, etc.

The organisms causing acute bacterial meningitis in India, based on a few reports in Indian literature [included are series with sample size > 50 and only the cerebrospinal fluid (CSF) culture positive cases] and occurring in varying frequency (percentage out of culture positive cases only) are as follows: *S. pneumoniae* (3.1–44.7%), *Staphylococcus aureus* (11.11–31.3%), *Neisseria meningitides* (3.1–21.2%), *Haemophilus influenzae type b* (9.4–26%), *S. aureus* (1.5–11.11%), *Klebsiella pneumoniae* (1.5–6.9%), *Citrobacter freundii* (12.5%), Group. B. Streptococci (9.5%), *E coli* (3.1–7.5%), *Pseudomonas aeruginosa* (1.5–6%), alpha hemolytic *Streptococcus* (0.74–5.5%), *Morexella* spp (5.5%), anaerobes (5.5%), *Salmonella typhimurium* (3–3.1%), *micrococci* (3.1%), *Streptococcus pyogenes* (3.1%), *Acinetobacter* spp (3.1%), *Proteus rettgeri* (3.1%), *Salmonella havana* (3.1%), Group B beta hemolytic *Streptococcus* (1.48%), *Proteus* (1.4%). It is important to note that culture positivity (which is the gold standard for etiological diagnosis) in all these studies are poor varying from 23.5% to 68.5%, majority hovering around 30%. All these organisms occur sporadically; *N. meningitides* is known to cause epidemics off and on.

PATHOGENESIS AND PATHOLOGY

There is varying degree of inflammation of the leptomeninges. The bacteria gain entry into the meninges through different routes namely (1) hematogenous, (2) contiguous, (3) direct implantation and (4) malformations having communication with CSF space. Hematogenous route is the most common route; the blood stream infection usually occurs as a part of a generalized bacteremia and septicemia without any definite focus or from some focus of infection elsewhere in the body like pyoderma, abscess, pharyngotonsillitis, bacterial endocarditis, osteomyelitis and otitis media. Infection through contiguity is seen in scalp cellulitis and abscess, mastoid abscess, osteomyelitis of scalp bones and vertebrae. Direct implantation can occur in scalp fracture, fracture cribriform plate, vertebral fracture. Recurrent pyogenic meningitis is often associated with congenital malformations, shunts and fracture of the cribriform plate and following cochlear implants.

The pathologic hallmark of pyogenic meningitis is accumulation of purulent exudate in the subarachnoid space over the cerebral hemispheres, sulci, gyri, base of the brain and basal cisterns. There is edema of the brain involving the white matter, compressed ventricles or at times dilated ventricle (due to obstruction of the CSF flow by exudates). Purulent exudate often shows bacteria and extends into cortex, cerebellum, brainstem, spinal cord along perivascular spaces. Choroid plexus shows purulent material.

The inflammatory exudate frequently engulfs/damages the meningeal, cortical and subcortical blood vessels causing thrombosis, impairing cerebral circulation. This often results in focal necrosis that may get infected resulting focal micro-abscesses. Vascular occlusion can also result from small infective microthrombi. The inflammatory exudate frequently engulfs/damages cranial nerves coming out of the brain. One immediate net effect of the inflammation and exudation is intracranial hypertension with its ill effects. Invasion of the leptomeninges by bacteria is associated with breach of the blood brain barrier and a cascade of body's reactionary defense mechanisms occur.

All these result in severe alteration in cerebral metabolism and homeostasis. Studies of the pathophysiology of bacterial meningitis have suggested that the development of neuronal injury is related to the release of vasoactive substances or alteration of blood-brain barrier permeability. Cerebral edema, increased intracranial pressure (ICP), systemic hypotension, decreased cerebral perfusion pressure, vascular inflammation, thrombosis and a variety of other vascular changes may result in global or regional reductions in cerebral blood flow (CBF), which contribute to this insult. Approximately one-third of infants and children with bacterial meningitis will have markedly reduced CBF, and even in those children with normal total flow, regional hypoperfusion is common. Reduced CBF is associated with cerebral edema and a poor prognosis.

Cerebral damage can affect various areas of the gray matter, white matter, cerebral pathways resulting in variety of sequelae. Hydrocephalus can develop secondary to obstruction to CSF circulation due to adhesion and fibrosis in the communicating canals (obstructive hydrocephalus) or secondary to reduced absorptive surface in pia-arachnoid (communicating hydro-cephalus).

CLINICAL MANIFESTATIONS

Common presenting *symptoms* are fever, seizures, abnormal behavior, refusal to feed and vomiting. The most important *signs* are (1) altered sensorium and (2) classic signs of meningeal

irritation. Altered sensorium can manifest as irritability, lethargy, obtundation, stupor and coma. At times the child may be delirious and makes shrill cry. The signs of *meningeal irritation,* i.e., neck rigidity, Kernig sign and Brudzinski sign are seen in varying frequency.

Signs of *intracranial hypertension* include headache, vomiting, papilledema, cranial nerve palsy (commonly 3rd, 4th and 6th nerve), hypertonia, hyper-reflexia, extensor plantar response, frequent vomiting (often forceful) and seizures. Bulged anterior fontanel is a very good sign of intracranial hypertension in infants if it is open. Features of herniation should be carefully looked for (dilated pupil, cranial nerve palsy, irregular respiration, continuous depression of sensorium). Brainstem herniation can cause death, which may be precipitated by lumbar puncture.

Focal deficits are also not seen uncommonly at presentation— like cranial nerve palsy, hemiplegia, paraplegia, etc. *Hypertension* is usually due to intracranial hypertension. *Hypotension* is usually seen in association with sepsis and dehydration. *Shock* may result from septicemia, dehydration, severe intracranial hypertension or a combination of these factors. Shock is common in meningococcemia often associated with adrenal involvement.

Other *nonspecific signs* of infection include fever and tachycardia. Features of associated diseases like pneumonia, diarrhea, pyoderma and otitis media can be seen and may mislead the clinician regarding the correct diagnosis. Certain clinical findings can give etiologic clue and should be kept in mind, i.e., rash (meningococcal meningitis), pneumonia (pneumococcal meningitis), otitis media (*H. influenzae* type B/pneumococcal meningitis), pyoderma, cellulitis, boils (staphylococcal meningitis), immunodeficiency disorder (*Pseudomonas* and other uncommon organism).

DIAGNOSTIC INVESTIGATIONS

Essential investigations are (1) CSF examination to demonstrate inflammation of the meninges and (2) recovery of the organism causing the inflammation through culture of CSF and Gram stain. Confirmed diagnosis however rests only on recovery of the bacteria from CSF.

The CSF is often turbid to varying extent, total cell count is raised with predominance of polymorphonuclear cells, protein is raised and sugar is low. Chloride may be normal to low depending upon status of hydration and vomiting. Most important and almost consistent diagnostic pointers in CSF are marked polymorphonuclear pleocytosis and low sugar (supposed to be due to consumption by bacteria/increased utilization by cerebral tissue). CSF sugar is usually less than CSF to blood sugar ratio which is usually 66%. Recovery of the organisms is through CSF culture and Gram stain. CSF smear can give positive results in as much as about 60–90% cases in expert hands.

It is better to repeat the lumber puncture (LP) after 48–72 hours if the LP is traumatic. The CSF be examined as soon as possible within 30 minutes, otherwise cells may degenerate and give fallacious count. Chances of getting a positive culture also may be reduced as some bacteria may die in external environment. Delayed inoculation into the culture media also may reduce the chances of growth. In India CSF culture positivity rate is usually low in most of the reported studies probably due to prior use of antibiotic and suboptimal laboratory techniques. Multiplex polymerase chain reaction is a promising new technique for etiological diagnosis of pyogenic meningitis.

Blood culture is essential in all cases. Other diagnostic aids are based on serology and antigen detection techniques. Currently the most useful ones are latex agglutination and PCR. These however cannot be a substitute for culture as they cannot give the antibiotic sensitivity of the pathogen, which is important for treatment.

The total leukocyte count (TLC) is usually high with polymorphonuclear leukocytosis and raised ESR. C-reactive protein (CRP), procalcitonin (PCT) and nonspecific markers of infection are often quite high and may help in differentiating it from viral and tubercular meningitis. Neuroimaging (CT or MRI) can detect intracranial hypertension, subdural effusion and empyema, ventriculitis, hydrocephalous, infarct, and abscess.

DIFFERENTIAL DIAGNOSIS

The most important conditions that need to be differentiated are viral *meningitis* and *encephalitis. Complex febrile convulsions* can look like pyogenic meningitis. However, a nontoxic look and normal to mildly altered sensorium that recovers quickly strongly points towards CFS. *Cerebral malaria* can mimic pyogenic meningitis at times; endemicity, presence of splenomegaly, no sign of meningeal irritation points towards it. *Brain abscess* may have focal features and often papilledema. Stroke following upper respiratory infection often with fever also may mimic pyogenic meningitis; again lack of sign of meningeal irritation, less toxicity, focal deficit with clear localization (hemiplegia) right from onset and findings related to the etiology like splenomegaly, murmur are pointers towards stroke. Some cases of *tubercular meningitis* (TBM) may have acute onset like pyogenic meningitis (mostly those having some complication). TBM should be suspected in presence of history of contact, splenomegaly, lymphadenopathy and focal deficit; detail history usually reveals duration of illness to be longer.

Analysis of the CSF is helpful diagnosis of viral meningitis and TBM in most cases. The most important findings in CSF in viral meningoencephalitis are lymphocytic pleocytosis and normal sugar and sterile culture and in TBM are lymphocytic pleocytosis, sugar that is low but not too low, and sterile culture. CSF sugar can be low in mumps meningoencephalitis and Japanese encephalitis. The CSF can be hemorrhagic at times in herpes simplex encephalitis. It needs to be noted that in practice CSF finding often show quite a lot of variability from normal creating difficulty in etiologic diagnosis, i.e., whether it is really pyogenic meningitis, viral meningitis or TBM. In some cases of pyogenic meningitis protein or sugar may be normal and even it may be acellular. In a series on meningitis having only CSF culture positive cases (n = 100), protein was normal in 22 (22%), sugar was normal in 21%, CSF was acellular in many but culture grew organisms.

TREATMENT

Antibiotic Therapy

Instituting treatment of pyogenic meningitis is considered as a medical emergency as it has been well established that later the antibiotic treatment, poorer is the outcome. The odds for unfavorable outcome may increase by up to 30% per hour of treatment delay. Hence, it is the practice to start antibiotic empirically once pyogenic meningitis is diagnosed without waiting for culture reports. Antibiotic therapy is subsequently modified after receiving the culture reports.

Initial Empirical Therapy

It is started with antibiotics that cover the most common bacteria and have good penetration into the CSF space. This can be achieved by third generation antibiotics cefotaxime and ceftriaxone. In infants beyond neonatal period and till about 3 months of life gram-negative organisms are common. It is usual to start cefotaxime and aminoglycosides like gentamicin/amikacin in

this age group. Doses of commonly used antibiotics for pyogenic meningitis are provided in **Box 1**.

Development of antibiotic resistance is a problem and has to be always kept in mind and changes have to be made accordingly. In USA *S. pneumoniae* has shown some resistant to cefotaxime and ceftriaxone in about 25% of isolates. Because of this it is often a practice to add vancomycin right from beginning in the empiric therapy. In India such resistance has not been reported.

If the meningitis is suspected to be due to *S. aureus* then vancomycin is added to the empirical therapy. If *Pseudomonas* is suspected ceftazidime is a good choice. Other antibiotics that are effective against some or other bacteria causing pyogenic meningitis should be kept in mind in cases of development of resistance or unsatisfactory response as these may have to be added under specific circumstances. Some such antibiotics that have been used in pyogenic meningitis are methicillin (*Staphylococcus*), nafcillin (*Staphylococcus*), meropenem (difficult cases), ampicillin (Group B *Streptococcus*, *Pneumococcus*, *Meningococcus*, some strains of *H. influenzae*, and *Listeria. monocytogenes*) and chloramphenicol (*H. influenzae, Salmonella*). Penicillin G (*S. pneumoniae*, *Meningococcus*), is practically not used due to difficult administration, side effects and development of resistance.

Duration of Antibiotic Therapy

Usually 10 days are believed to be sufficient in most children with uncomplicated pyogenic meningitis who show a good response to treatment. If response is not satisfactory it is a practice to continue antibiotic longer or modify treatment after repeating LP. Longer duration of treatment (2–3 weeks) is preferred in gram-negative and *Staphylococcus* infections. However, if clinical condition is satisfactory and CSF is sterile antibiotic can be stopped earlier. Prolonged duration of therapy up to 4–6 weeks may be indicated for subdural empyema and ventriculitis.

Repeat LP is usually not needed in uncomplicated pyogenic meningitis. It is prudent to do a repeat CSF examination if response is unsatisfactory after about 72 hours; if CSF shows deterioration specially showing increased cellularity, antibiotic is often revised at this point.

Revision of antibiotic after starting the empirical therapy is done on the basis of culture and sensitivity report. In culture negative cases if there is no response or deterioration in clinical condition, antibiotic may be revised keeping in mind the culture sensitivity pattern of the suspected pathogen.

Supportive Treatment

During acute stage the complications—*dehydration, electrolyte disturbance, seizures, respiratory failure and shock* have to be managed appropriately. Fluid therapy should be tailored according to the hydration status and presence of raised intracranial pressure. There is no need for routine fluid restriction. As per a Cochrane review some evidence supports giving full maintenance intravenous fluids rather than restricted in the first 48 hours, in settings with high mortality rates and where patients present late.

Intracranial hypertension needs to be handled properly; mannitol and dexamethasone are commonly used. *Subdural effusion/empyema* usually does not need additional treatment except if it causes marked intracranial hypertension when tap has to be done.

H. influenzae type B and *S. pneumoniae* meningitis have been shown to be associated with significant hearing loss. Corticosteroids significantly reduced severe hearing loss in children with *H. influenzae* meningitis (RR 0.34, 95% CI 0.20–0.59) but not in children with meningitis due to non-Haemophilus species; it also reduced neurological sequelae, but did not reduce overall mortality. No significant adverse effect was seen except recurrence of fever. Dexamethasone (0.15 mg/kg/dose IV 6 hourly for 4 days) thus should be administered first dose starting before the first dose of antibiotic if meningitis is suspected to be due to *H. influenzae*. With increased thrust of immunization with HiB vaccine the role of dexamethasone is limited

Routine/daily monitoring should include general condition, vital signs, mental status with GCS, appearance of new signs, status of hydration and feeding, fluid, electrolytes and output. Cranial USG that can be done easily is a very useful tool for objective monitoring. During prolonged antibiotic therapy it is important to monitor for side effects like drug rash, renal functions (vancomycin), and USG for gall stone (ceftriaxone). Keeping in mind the complication of hearing loss, all patients at discharge should undergo hearing test; this may help appropriate rehabilitation of some cases.

OUTCOME

Mortality in bacterial meningitis seems to vary from 10% to 30% based on a few reported studies from India. In USA it is around 1–5% at present. Sequelae include a variety of neurodevelopmental, cognitive and motor dysfunctions like mental insufficiency (often subtle), learning disorders, speech, hearing and visual disorders, and behavior problems. These complications need to be managed appropriately.

PREVENTION

Vaccines against *H. influenzae* (Hib), *S. pneumoniae* and *N. meningitidis* have been introduced in many countries. Hib vaccine has proven to be most effective. In USA where Hib vaccine is a part of the routine infant immunization schedule, *H. influenzae* has now been virtually eradicated as a cause of childhood meningitis. Vaccines have also been introduced for pneumococcal infections and seem to be quite promising. Vaccination aimed at reducing *N. meningitidis* infection is under evaluation.

Prophylactic strategy aimed at preventing development of meningitis by these common organisms in contacts is in place and should be followed. Rifampicin prophylaxis (20 mg/kg/day for 4 days) is given to all household contacts of *H. influenzae* meningitis. Chemoprophylaxis with rifampicin (10 mg/kg/dose) every 12 hours for 2 days should be given to close contacts in cases of *N. meningitidis*.

MORE ON THIS TOPIC

Aggarwal M, Manchanda V, Talukdar B. Meningitis due to Neisseria meningitidis serogroup B in India. Indian Pediatr. 2013;50:601-3.

Agrawal S, Nadel S. Acute bacterial meningitis in infants and children: epidemiology and management. Pediatr Drugs. 2011;13:385-400.

Ashwal S, Tomasi L, Schneider S, et al. Bacterial meningitis in children: pathophysiology and treatment. Neurology. 1992;42:739-48.

Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2013;6:CD004405.

Chinchankar N, Mane M, Bhave S, et al. Diagnosis and outcome of acute bacterial meningitis in early childhood. Indian Pediatr. 2002;39:914-21.

BOX 1 Doses of the common antibiotics for pyogenic meningitis

- Cefotaxime 200 mg/kg/day divided 6 hourly
- Ceftriaxone 100 mg/kg/day diveded 12 hourly
- Ceftazidime 150 mg/kg/day 6 hourly
- Vancomycin 60 mg/kg/day divided 6 hourly
- Ampicillin 300 mg/kg/day divided 6 hourly
- Amikacin 15 mg/kg/day divided 8 hourly
- Gentamicin 7.5 mg/kg/day divided 8 hourly
- Meropenem 120 mg/kg/day divided 8 hourly.

Damodaran A, Aneja S, Malhotra VL, et al. Sensorineural hearing loss following acute bacterial meningitis—a prospective evaluation. Indian Pediatr. 1996;33:763-6.

Dubos F, Martinot A, Gendrel D, et al. Clinical decision rules for evaluating meningitis in children. Current Opnion Neurol. 2009;22:288-93.

Feigin RD, Curter WB. Bacterial meningitis beyond the neonatal period. In: Feigin RD, Chery JD, Demmler-Harrison GJ, Kaplan SA. Textbook of Pediatric Infectious Disease. 6th ed. Philadelphia: Saunders; 2014. pp. 439-71.

Fule RP, Powar RM, Saoji AM. Bacteriological profile of acute pyogenic meningitis. Indian Pediatr. 1989;26:174-5.

Maconochie I, Baumer H, Stewart ME. Fluid therapy for acute bacterial meningitis. Cochrane Database Syst Rev. 2008;1:CD004786.

Mahajan R, Lodha A, Anand R, et al. Cranial sonography in bacterial meningitis. Indian Pediatr. 1995;32:989-93.

Mirdha BR, Gupta U, Bhujwala RA. Latex agglutination test: an adjunct to the laboratory diagnosis of pyogenic bacterial meningitis. Indian J Pediatr. 1991;58:521-24.

Narkeviciute I, Bernatoniene J, Mikelionyte A, et al. Aetiological diagnostics of acute bacterial meningitis in children. Cand J Infect Dis. 2006;38:782-7.

Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis. 2002;186 (Suppl 2):S225-33.

Singhi S, Singhi P, Baranwal AK. Bacterial meningitis in children: critical care needs. Indian J Pediatr. 2001;68:737-47.

Talukdar B, Khalil A, Sarkar R, Saini L. Meningococcal meningitis clinical observations during an epidemic. Indian Pediatr. 1988;25:329-34.

Talwar R, Talukdar B, Gupta NC, Rath B. Ultrasonographic study in meningitis. Indian Pediatr. 1993;30:1225-7.

IN A NUTSHELL

1. About 90% of the cases of pyogenic meningitis are caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and *Neisseria meningitidis*.
2. The bacteria gain entry into the meninges by hematogenous route, contiguous spread, direct implantation, and through malformations having communication with CSF space.
3. The pathologic hallmark of pyogenic meningitis is accumulation of purulent exudate in the subarachnoid space over the cerebral hemispheres, sulci, gyri, base of the brain and basal cisterns.
4. Common presenting symptoms are fever, seizures, abnormal behavior, refusal to feed and vomiting. The most important signs are altered sensorium and classic signs of meningeal irritation.
5. Signs of intracranial hypertension include headache, vomiting, papilledema; 3rd, 4th and 6th, cranial nerve palsy, hypertonia, hyperreflexia, extensor plantar response and seizures.
6. The CSF is often turbid to varying extent, total cell count is raised with predominance of polymorphonuclear cells, protein is raised and sugar is low.
7. Initial empirical therapy is started with third generation antibiotics (cefotaxime or ceftriaxone). Treatment is given intravenously for minimum 10 days.

Chapter 42.16
Tuberculosis of the Central Nervous System
Chandrakanta, Rashmi Kumar

Central nervous system tuberculosis (CNS TB) is a devastating illness which carries a high mortality and morbidity. Disease is caused by *Mycobacterium tuberculosis* and primarily affects young children. Co-infection with human immunodeficiency virus (HIV) and the emergence of drug resistant strains further complicates the picture.

BURDEN OF DISEASE

About 1% of total TB cases and 5–10% of extra pulmonary TB cases develop CNS tuberculosis. Incidence is higher in young children and HIV infected patients. The estimated mortality of tuberculous meningitis in India is about 1.5 per 100,000 population. Risk factors for CNS tuberculosis include younger age, HIV co-infection, malnutrition, recent measles or pertussis infection, the use of immunosuppressive agents and high disease prevalence in the community.

PATHOGENESIS

According to the widely accepted theory, CNS tuberculosis occurs as a result of secondary hematogenous spread from the site of primary extracranial tuberculous lesion, which is frequently in the lung, and not because of direct hematogenous spread. This secondary hematogenous spread occurs early in infection before adaptive immune responses control the infection. Rich and Mc Cordock in 1933 suggested a two stage model. Small tuberculous lesions (Rich's foci) develop around bacteria seeded in the brain during the initial hematogenous dissemination. These initial foci may be in the meninges, the subpial or subependymal surface of the brain or the spinal cord and are most commonly situated in the sylvian fissure. These foci may remain dormant for years after initial infection. Subsequent rupture or growth of these foci results in various type of CNS tuberculosis. Rupture into the subarachnoid space or into the ventricular space leads to meningitis. Sizeable inoculation or absence of an adequate cell-mediated immunity is thought to be the cause of parenchymal cerebral tuberculous foci developing to tuberculoma or tuberculous brain abscess. How the bacteria leave the lung, enter the brain and cause cerebral pathology is not clear.

Immunological factors are probably responsible for the rupture or growth of these foci. A lower number of CD4 T lymphocytes have been found in children with tuberculous meningitis (TBM) as compared to children who had primary pulmonary complex only. Recently association of distinct *Mycobacterium tuberculosis* strains with CNS disease has been found. Indo-Oceanic or East Asian Beijing lineages are more likely to cause meningitis than Euro-American lineages. A bacterial gene known as *pknD*, that encodes for serine/threonine protein kinase required for invasion of cells lining the brain endothelium has been identified.

CLASSIFICATION OF NEUROTUBERCULOSIS

Neurotuberculosis has a wide range of presentations, including tuberculous meningitis, tuberculoma, tuberculous abscess, spinal TB and tuberculous encephalopathy. Out of these TBM is the most common form, found in 70–80% of the cases of neurotuberculosis. Classification of CNS tuberculosis is given in **Table 1**.

Table 1 Classification of CNS tuberculosis

Intracranial	Tuberculous meningitis
	Serous tuberculous meningitis
	Tuberculous encephalopathy
	Tuberculous vasculopathy
	Localized tuberculous meningitis
	CNS tuberculoma (single or multiple)
	Tuberculous brain abscess
Spinal	*Osseous spinal TB*
	Pott's spine and Pott's paraplegia
	Nonosseous spinal TB
	Spinal tuberculoma
	Isolated spinal TBM
	Tuberculous radiculomyelopathy (usually associated with TBM)

Abbreviations: CNS, central nervous system; TB, tuberculosis; TBM, tuberculous meningitis.

TUBERCULOUS MENINGITIS

It usually occurs within the first 3–6 months after the primary infection. After the release of tubercle bacilli from granulomatous lesions into the subarachnoid space, dense gelatinous exudates are formed predominantly around the sylvian fissures, basal cisterns, brainstem and cerebellum. It is hypothesized that these exudates are localized to the basilar areas simply as a result of the normal flow pattern of CSF. Of note, Rich foci typically follow the vascular pattern and they are not preferentially distributed to the basilar areas of the brain where the exudates are typically located. Direct contact of the exudates leads to a border zone reaction in the underlying brain parenchyma. Blockage of CSF pathways is responsible for the development of hydrocephalus in TBM. This blockade can be at basal cisterns, outflow of 4th ventricle or cerebral aqueduct. Commonly it is due to (1) blockage of the basal cisterns and medullocerebellar angles causing obstruction to the flow of the CSF in the subarachnoid spaces by dense basal exudates and/or (2) interference in the absorption of CSF by the arachnoid granulations. Aqueduct is usually dilated but sometimes it can be occluded because of compression by edematous portion of midbrain or tuberculoma or exudates and edema.

Vascular involvement is common and occurs because of inflammation, thrombosis or external compression by exudates. Vasculitis develops in the vessels of the circle of Willis, the vertebrobasilar system and the perforating branches of the middle cerebral artery resulting in infarctions in the distribution of these vessels. Vessels of the circle of Willis are more frequently involved than the vessels of the basilar system. Sylvian fissure and the basal ganglion are the most common sites of infarction. Infarctions are located in the distribution of medial striate and thalamo-perforating arteries in majority of patients. Cranial nerves are involved as a result of entrapment neuropathy caused by thick exudates.

Clinical Presentation

Early diagnosis of TBM is difficult because of nonspecific clinical features, and disease is often diagnosed late when brain damage has already occurred. In children peak incidence is between 2 years and 4 years and it is unusual below 6 months of age. Youngest case reported was a 3 months old child.

Typically TBM has a subacute onset with a gap of 1–4 weeks or more between onset of fever and the onset of neurological symptoms. Early symptoms are nonspecific and include poor weight gain, low-grade fever, vomiting, photophobia and listlessness. Headache occurs less often than the adults. As the

disease progresses meningeal irritation signs, altered sensorium, seizures, signs of raised intracranial pressure, cranial nerve palsies, focal deficits, and abnormal movements are seen. **Table 2** shows common clinical features at presentation of TBM. A family history of tuberculosis can be identified in about half of children. Cranial nerve palsies are found in 30–50% cases and sixth nerve is most commonly involved. Vision loss can occur due to optochiasmatic arachnoiditis, third ventricle compression of optic chiasma or optic nerve granuloma. Fundoscopy may reveal papilledema and choroid tubercles. Choroid tubercles are mostly associated with miliary tuberculosis and found in only 10% cases without miliary tuberculosis. These are yellow lesions with indistinct borders (single or cluster) and are virtually pathognomonic of tubercular etiology. Grading of the severity of TBM according to modified British Medical Research Council (1948) clinical criteria is given in **Table 3**.

Diagnosis of TBM can neither be made nor excluded on the basis of clinical features alone but they are helpful in making the diagnosis. In a study in children it was found that persisting fever for more than 6 days, optic atrophy, focal neurologic deficit, abnormal movements, and CSF leukocyte differential of less than 50% neutrophils were the clinical variables predictive of TBM. The diagnostic sensitivity and specificity were 98% and 44% respectively when one feature was present. When three or more features were present sensitivity was 55% and specificity was 98%. For adult patients of TBM in Vietnam diagnostic rule was developed which has reported sensitivities of 96–98% and specificities ranging from 68% to 88%.

Two uncommon forms of TBM are serous TB meningitis and TB encephalopathy.

Serous TBM
Serous TBM is characterized by signs and symptoms of mild meningitis seen especially in BCG vaccinated children. These children present with fever, headache and vomiting and may be conscious at the time of presentation. Disease is mostly localized and CSF examination is normal. A study on 107 bacteriologically proven TBM cases found a normal CSF in 15% cases.

Table 2 Tuberculous meningitis clinical features on presentation

Clinical feature	Percentage
Headache	50–80%
Fever	60–95%
Vomiting	30–60%
Photophobia	5–10%
Anorexia	60–80%
Neck stiffness	40–80%
Confusion	10–30%
Coma	30–60%
Any cranial nerve palsy	30–50%
Cranial nerve III palsy	5–15%
Cranial nerve VI palsy	30–40%
Cranial nerve VII palsy	10–20%
Hemiparesis	10–20%
Paraparesis	5–10%
Seizures	50%

Table 3 Severity of tuberculous meningitis (Modified MRC scale)

Stage I	Alert and orientated without focal neurological deficit
Stage II	Glasgow coma score 14–10 with or without focal neurological deficit or Glasgow coma score 15 with focal neurological deficit
Stage III	Glasgow coma score less than 10 with or without focal neurological deficit

From: van Toorn R, Springer P, Laubscher JA, Schoeman JF. Value of different staging systems for predicting neurological outcome in childhood tuberculous meningitis. Int J Tuberc Lung Dis. 2012;16(5): 628-32.

Tuberculous Encephalopathy
This variant of cerebral tuberculosis has been reported in Indian children with diffuse cerebral disorder. Presenting symptoms were coma, convulsions, involuntary movements and pyramidal signs with normal CSF findings. Postmortem examination of brain showed diffuse cerebral edema, perivascular myelin loss and sometimes hemorrhagic leukoencephalopathy. These features may be more typical of a postinfectious allergic encephalomyelitis. Other postulations are hypersensitivity to tuberculous protein, isoimmunization, and cerebral microangiopathy. Few reports suggest that disease is responsive to corticosteroid treatment but no controlled trial has been done.

Differential Diagnosis
Many CNS infections have presentation similar to tuberculous meningitis. In particular TBM may be confused with partially treated pyogenic meningitis, viral encephalitis, typhoid encephalopathy, brain abscess, brain tumor and chronic subdural hematoma. These should be ruled out by appropriate investigations as required. Diagnostic criteria for the classification of definite, probable or possible tuberculous meningitis on the basis of clinical features, CSF findings, neuroimaging and other laboratory tests have been used, mainly for research purposes.

Laboratory Diagnosis
Cerebrospinal fluid (CSF) examination and neuroimaging are helpful in confirmation of diagnosis of TBM **(Box 1)**. CSF examination typically shows predominantly lymphocytic reaction (50–500 white cells per mL) with raised protein levels (0.8–4 g/L). CSF sugar is low, mostly less than two-thirds of serum glucose concentration. CSF lactate is about 5–10 mmol/L. In early TBM polymorphonuclear cells may be predominant, which is replaced by lymphocytes later on. CSF profile of TBM mimics a large list of infectious and noninfectious meningitic processes.

Definite diagnosis requires demonstration of tubercle bacilli in the CSF either by smear examination with Ziehl-Neelsen stain (sensitivity 10–25%) or by bacterial culture (sensitivity 18–83%). Ventricular fluid has highest detection rate of positivity. HIV infected individuals have more number of tubercular bacilli in CSF than noninfected individuals so positivity is higher. Following methods increase the yield of CSF smear examination—examination of at least 10 mL CSF, repeated samples examination, CSF taken before or shortly after starting treatment, centrifuging at

BOX 1 List of investigations to diagnose central nervous system tuberculosis

1. Laboratory diagnosis (CSF sample):
   a. CSF microscopy and CSF protein and sugar estimation
   b. ZN staining for acid fast bacilli
   c. Culture and sensitivity for *Mycobacterium tuberculosis*
   d. ISMA
   e. NAAT and other PCR assays (e.g., INNO-LiPA Rif.TB and Xpert MTB/RIF)
2. Neuroimaging––MRI/CT scan of brain/spine
3. Tests to detect evidences of tuberculosis elsewhere in the body:
   a. Chest X-ray
   b. Tuberculin test
   c. *M. tuberculosis* AFB stain/culture from another source (i.e., sputum, lymph node, gastric lavage, etc.)
   d. Commercial *M. tuberculosis* NAAT from extra-neural specimen
   e. CT/MR/ultrasound evidence for TB outside the CNS

Abbreviations: CSF, cerebrospinal fluid; ISMA, immunocytochemical staining of mycobacterial antigens; AFB, acid-fast bacillus; NAAT, nuceic acid amplification test; PCR, polymerase chain reaction; CNS central nervous system

relative high centrifugal force for 20 minutes, careful examination for at least 10–20 minutes. A thorough investigation should be done to isolate acid-fast bacillus (AFB) from other sites like gastric aspirate, fine needle aspiration of lymph node and peritoneal or pleural fluid.

Use of the immunocytochemical staining of mycobacterial antigens (ISMA) in the cytoplasm of CSF macrophages has shown some promising results. It is based on the assumption that in initial stage of infection, bacilli are ingested by the macrophages and during the second stage bacilli grow logarithmically within newly recruited macrophages. Consequently, the positivity of the test indicates that viable *M. tuberculosis* isolates are present in CSF. A study has demonstrated its sensitivity of 73.5% and specificity of 90.7% with positive and negative predictive values of 52.9% and 96.0% respectively.

As it is difficult to detect tubercle bacilli in the CSF, a number of other tests have been developed. These tests include the evaluation of adenosine deaminase activity (ADA), interferon-gamma (IFN-γ) release by lymphocytes, and *M. tuberculosis* antigens and antibodies.

The ADA activity test is a rapid test that represents the proliferation and differentiation of lymphocytes as a result of the activation of cell-mediated immunity after *M. tuberculosis* infection. In patients with TBM, it was found that ADA activity could not distinguish between TBM and other types of bacterial meningitis, but that it could help once meningitis due to different pathogens has been ruled out. ADA values from 1 to 4 U/L (sensitivity > 93% and specificity < 80%) can help to exclude TBM and values more than 8 U/L (sensitivity < 59% and specificity > 96%) can improve the diagnosis of TBM ($p < 0.001$).

Measurement of IFN-γ release by lymphocytes stimulated by *M. tuberculosis* antigens has been found useful for the diagnosis of latent TB and extrapulmonary TB. However, in TBM it has shown variable results from study to study. Liao et al. found that the test was 100% sensitive and 100% specific, whereas other authors reported a very poor value of the test in diagnosing TBM.

Tests which detect mycobacterium specific antigen and antibodies in CSF are rapid and less expensive but have poor sensitivity and specificity. Also, these tests can not differentiate acute from the past infection. For the antibody assay sensitivity and specificity are 52–93% and 58–99% respectively. Detection of various *M. tuberculosis* antigen markers, such as lipoarabinomannan, purified protein derivatives, heat shock protein of 62 kDa and 14 kDa, GroE, Ag 85 complex and 38 kDa antigen have been tried to confirm TBM diagnosis. For various antigen assays reported sensitivity and specificity are 38–94% and 95–100% respectively.

Commercially available nucleic acid amplification test (NAA) and other polymerase chain reaction (PCR) assays are rapid tests but sensitivity and specificity depends on the primer used for the test. When primer against IS 6110 is used for PCR, sensitivity is 76% and specificity is 89%. A systematic review concluded that commercial NAA assay can confirm TBM (98% specificity) but cannot rule it out (sensitivity 56%). Xpert MTb/RIF assay have been used for rapid diagnosis of TBM (sensitivity 67–85% and specificity of 94–98%).

NEUROIMAGING

Neuroimaging is helpful in both diagnosis and management of TBM. Magnetic resonance imaging (MRI) of brain is superior to a CT scan particularly when brainstem is involved. Diffusion weighted MRI can detect early infarcts and border-zone encephalitis (cytotoxic edema that underlies the tuberculous exudates). Leptomeningeal tubercles are visualized in about 90% of children by the Gadolinium enhanced MRI. Magnetic resonance imaging is also valuable for the identification and monitoring of associated cranial neuropathies like optochiasmatic arachnoiditis requiring urgent treatment. MR angiography can be used to identify vascular involvement.

CT scan brain may be normal in up to 30% cases of early TBM but abnormal in most of cases with late TBM. CT scan reveals hyperdense basal exudates in noncontrast film **(Fig. 1)**. Contrast enhanced film shows basal meningeal enhancement, infarcts, hydrocephalus and tuberculomas. A study revealed that basal meningeal enhancement, ventriculomegaly, tuberculoma, and infarcts as characteristics to distinguish CNS tuberculosis from pyogenic meningitis and proposed that basal meningeal enhancement, tuberculoma, or both were 89% sensitive and 100% specific for TBM.

TREATMENT OF CNS TUBERCULOSIS

Medical Management

Chemotherapeutic regimens for TBM are based on expert opinion rather than evidence. Most of the guidelines follow a model of treatment of pulmonary tuberculosis. Different treatment regimens for treatment of TBM are given in **Box 2**. Rifampicin, isoniazid,
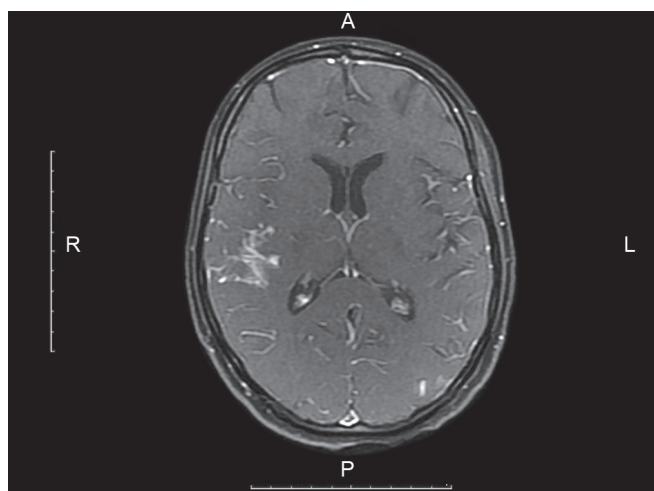
Figure 1 Meningitis with thick exudates and mild hydrocephalus

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BOX 2 Treatment of central nervous system tuberculosis

1. Supportive treatment (particularly in TBM cases)
   a. Maintenance of airway breathing and circulation
   b. Intravenous fluid therapy—Isotonic fluids like dextrose normal saline
   c. Maintenance of acid base and electrolyte balance
   d. Antiepileptic drugs for control of seizures
   e. Treatment of raised intracranial pressure-–-intravenous mannitol/3% saline infusion, acetazolamide, glycerol and diuretics. In refractory cases hyperventilation and urgent surgical intervention should be considered.
   f. Prevention of other complications in a comatose child, e.g., exposure keratitis, aspiration pneumonia, bed sore etc.
2. Specific treatment—Antituberculous therapy along with corticosteroid treatment (various guidelines are given in **Table 5**)
3. Surgical treatment
   a. Ventriculoperitoneal shunt or endoscopic third ventriculotomy for hydrocephalus if indicated
   b. Surgical decompression in case of Pott's paraplegia
   c. In case of large tuberculoma causing mass effect and tuberculous brain abscess

Abbreviation: TBM, tuberculous meningitis.

pyrazinamide and ethambutol are the main drugs used for TBM treatment. Pyrazinamide and isoniazid are freely distributed in CSF. Rifampicin, ethambutol and streptomycin do not enter CSF but may penetrate inflamed meninges. In CNS tuberculosis daily therapy should be preferred particularly in intensive phase. Few observational studies have shown good results with intermittent drug therapy under DOTS program, but controlled trials have not been done. Current WHO guidelines state that TBM should be treated by 2RHZE followed by HR for 10 months. There are promising data to suggest that increasing the intensity of treatment, through use of high-dose intravenous rifampicin and the addition of moxifloxacin, can enhance bacterial killing and improvement in outcome. **Tables 4 and 5** show 1st line and 2nd line antituberculous drugs for CNS tuberculosis.

Multidrug-Resistant TBM

It is extremely difficult to suspect multidrug resistant (MDR) TBM except in a situation when a contact is a case of MDR TB. In high burden countries probability of a patient with TBM having MDR tuberculosis would be 0.1–1.4%. Association of MDR TBM with

Beijing strains and drug resistance related mutations in katG and rpoB genes has been found. Standard culture methods to test drug susceptibility are too slow to help in deciding treatment plan and most patients have usually died before results are available. Therefore CSF NAATs and detection of genetic mutations that confer drug resistance, e.g., Xpert MTB are the only way to diagnose drug resistance quickly.

In a study, fatality rate of MDR TBM was found 57% with significant functional impairment in most of the survivors. Isoniazid monoresistant disease requires addition of another drug with better CSF penetration. MDR TBM is treated with extended course of second line drugs. These drugs are less effective and have more side effects than a rifampicin and isoniazid based regimen. WHO guidelines recommend that an injectable drug (e.g., amikacin, capreomycin) with a fluoroquinolone (e.g., moxifloxacin), and at least two other active drugs should be used during initial phase of treatment of multidrug-resistant pulmonary tuberculosis. Choice of drug should be determined by probable susceptibility and CSF penetration. Because ethionamide and cycloserine have good CNS penetration, they

Table 4 Guidelines for the treatment of CNS tuberculosis in infants and children

Revised National Tuberculosis Control Program/ Indian Academy of Pediatrics (2010)	Rifampicin 10 mg/kg/day (max 600 mg) for 8–9 months Isoniazid 5–10 mg/kg/day (max 300 mg) for 8–9 months Pyrazinamide 30–35 mg/kg/day (max 2 g) for 2 months Ethambutol 20 mg/kg/day (max 1 g) for 2 months Prednisolone 2–4 mg/kg/day for 2–4 weeks followed by tapering doses for 2 weeks
British Infection Society (2009)	Isoniazid 10–20 mg/kg/day (max 500 mg) orally for 12 months Rifampin 10–20 mg/kg/day (max 600 mg) orally for 12 months Pyrazinamide 30–35 mg/kg/day (max 2 g) orally for 2 months Ethambutol 15–20 mg/kg/day (max 1 g) orally for 2 months Prednisolone 4 mg/kg/day orally for 4 weeks, followed by a reducing course over 4 weeks
American Thoracic Society, CDC, and Infectious Diseases Society of America (2006)	Isoniazid 10–15 mg/kg/day (max 300 mg) orally for 9–12 months Rifampin 10–20 mg/kg/day (max 600 mg) orally for 9–12 months Pyrazinamide 15–30 mg/kg/day (max 2 g) orally for 2 months Ethambutol 15–20 mg/kg/day (max 1 g) orally for 2 months Dexamethasone 8 mg/day/day orally for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more for 3 weeks, followed by a reducing course over 3 weeks
World Health Organization (2014)	Isoniazid 10 (7–15) mg/kg/day (max 300 mg) orally for 12 months Rifampin 15 (10–20) mg/kg/day (max 600 mg) orally for 12 months Pyrazinamide 35 (30–40) mg/kg/day (max 2 g) orally for 2 months Ethambutol 20 (15–25) mg/kg/day orally for 2 months Prednisone 2 mg/kg/24 hour orally for 4 weeks, followed by a reducing course over 1–2 weeks

Table 5 Recommended daily dosages of second-line anti-tuberculous drugs for treatment of tuberculous meningitis in infants and children

Name of drug	*Doses*	*CSF penetration*
Ethionamide	20 mg/kg/day (max 1 g) oral single dose	Good
Cycloserine	10–15 mg/kg/day (max 1 g) oral single daily dose	Good
Streptomycin	20–40 mg/kg/day (max 1 g) IM or IV single daily dose	Poor but penetrate inflamed meninges
Para-aminosalicylic acid	200–300 mg/kg/day orally in 2–4 doses	No data
Capreomycin	15–30 mg/kg/day (max 1000 mg) orally single daily dose	No data
Amikacin and Kanamycin	15–30 mg/kg/day (max 1 g/day) IM or IV as a single daily dose	Poor but penetrate inflamed meninges
Ofloxacin	15–20 mg/kg/day (max 800 mg) orally as a single daily dose	Not as good as levofloxacin and moxifloxacin
Levofloxacin	7.5–10 mg/kg/day (max 500 mg) orally single daily dose	Good
Moxifloxacin	7.5–10 mg/kg/24 hours (max 500 mg) orally single daily dose	Good
Ciprofloxacin	20–30 mg/kg/24 hours (max 1.5 g) orally single daily dose	Not as good as levofloxacin and moxifloxacin

may be used as part of *intensive-phase* treatment regimen in patients with suspected MDR TBM.

Corticosteroids in CNS TB

Role of corticosteroids in TBM is a controversial issue but a recent Cochrane systemic review concluded that addition of corticosteroid to the treatment reduced the risk of death and disabling residual neurologic deficit. Adverse events were less severe particularly hepatitis. So, it should be used irrespective of patient's age and stage of the disease except in HIV infection. In unstable patients intravenous dexamethasone may be added till oral steroids can be added by oral/nasogastric tube. In some patients response is dramatic with rapid improvement in headache, sensorium and CSF abnormalities. Some argue that corticosteroids by decreasing the meningeal inflammation will lead to decrease CSF penetration of antitubercular drugs. But, in a clinical trial use of corticosteroids did not reduce the CSF concentration of any of the antituberculous drugs.

Preliminary data suggest that the beneficial effect of adjunctive corticosteroids may be augmented by aspirin and predicted by a polymorphism in a gene responsible for eicosanoid synthesis. In a study aspirin resulted in insignificantly lesser number of strokes and significantly reduced 3 months mortality in patients with TBM. Thalidomide, which has an anti-inflammatory and immunomodulatory action, has been rarely used as adjunctive treatment in neurotuberculosis, especially in patients with tuberculous abscesses, tuberculous-related optochiasmatic arachnoiditis and nonresponding tuberculomas.

Treatment of Complications

Aggressive and appropriate management of raised intracranial pressure (ICP), hydrocephalus, vasculitis, acute seizures and hyponatremia can minimize the secondary brain injury.

Hyponatremia

Low serum sodium levels are found in 35–65% cases of TBM. Causes of hyponatremia in TBM include cerebral salt wasting syndrome (CSWS), syndrome of inappropriate antidiuretic hormone secretion (SIADH) and increased renal sensitivity to ADH. Hyponatremia is associated with increased mortality and morbidity in these children. Volume and sodium replacement is performed for the treatment of CSWS. Mineralocorticoid supplementation has also been shown to be effective. For SIADH fluid restriction is done and in case hyponatremia is severe, 3% normal saline along with furosemide is added.

Acute Seizures

Acute seizures occur in about 50% of children. Phenytoin is the most frequently used AED for acute management of seizures. Many antiepileptic drugs interact with antituberculous drugs and may affect metabolism of each other. Also, some antiepileptic drugs are hepatotoxic (sodium valproate) as are antitubercular drugs.

Vasculitis

Corticosteroids may be beneficial because of their anti-inflammatory effect.

Raised Intracranial Pressure (ICP)

Multiple factors are responsible for increased ICP and include cerebral edema due encephalitic process, infarcts with edema, hydrocephalus, tuberculomas and electrolyte disturbances. Osmotic agents like mannitol and hypertonic saline are used to lower the ICP particularly in those patients who do not require surgery.

Treatment of Hydrocephalus

Hydrocephalus is found in more than 80% of children with TBM at presentation. Clinical signs of raised intracranial pressure are poorly associated with presence of hydrocephalus on neuroimaging, so neuroimaging should be done in all children to exclude hydrocephalus. About 80% of children with communicating hydrocephalus can be managed by the medical treatment (acetazolamide and furosemide) only. Failed medical treatment and noncommunicating hydrocephalus are the indications for the ventriculoperitoneal shunting. Endoscopic third ventriculostomy has become an alternative surgical option to divert CSF flow without complications of shunt. Success rates of this procedure are roughly 65%. Failure of the procedure is often caused by distorted anatomy of the third ventricle floor and the fact that hydrocephalus presents during the acute phase of the disease, rather than being post infectious. However, there is no clear cut consensus about timing of CSF diversion surgeries. Many time arrest of hydrocephalus occur even in patients with gross hydrocephalus with medical treatment only.

Paradoxical Worsening During Treatment

Sometimes size of the tuberculomas or meningeal inflammation increases or new tuberculomas appears in TBM during treatment with antituberculous therapy. Mostly these are noticed accidentally by a follow up CT scan performed routinely or when new neurological signs develop during the course. Similar changes have been observed in isolated intracranial and spinal tuberculomas. Resolution of the lesions occurs with continued treatment and steroid therapy probably has a preventive role.

TBM in HIV Patients

Coinfection with HIV does not alter the clinical presentation of TBM, but number and nature of complications may be different. In these patients basal meningeal enhancement and hydrocephalus on CT scan are less common. They have higher number of bacilli in meninges so positivity of CSF AFB staining and culture is relatively high. Active extrameningeal tuberculosis is more common and case fatality rate is as high as 60%. Corticosteroids are not indicated with antituberculous drugs in HIV infected patients. If antiretroviral therapy is started early along with antitubercular drugs, chances of drug toxicity is increased and immune reconstitution inflammatory syndrome can develop. Delayed antiretroviral therapy could allow opportunistic infections to occur and complicate the picture. In a series of 34 patients, 16 developed immune reconstitution syndrome after a median duration of 14 days of starting antiretroviral drugs. Worsening headache and neck stiffness were the common manifestations. Corticosteroids are the mainstay of treatment of TBM associated IRIS, with interruption of antiretroviral therapy reserved for life threatening situation.

OUTCOME AND PROGNOSIS

Clinical stage of TBM at which treatment has been started is the single most important determinant of the outcome for survival and sequelae. Young age, malnutrition, hydrocephalus, focal neurological deficit, miliary disease, underlying debilitating disease and HIV infection are associated with bad prognosis. Mortality and morbidity is very low if treatment is started in stage I, while in stage III almost 50% of patients die, and survivors have some form of neurological deficit. Various sequelae occur in 10–85% of cases TBM. They are intellectual disability, epilepsy, neurological deficits, cranial nerve palsy (commonly 7th, 3rd and 6th cranial nerves), blindness, deafness, behavior problems, and hydrocephalus. Hypothalamic disturbances can lead to precocious

puberty, diabetes insipidus, obesity, Frolich syndrome and growth retardation later on. Intracranial calcifications which are detectable after 2–3 years are found in 20–48% of patients with TBM.

INTRACRANIAL TUBERCULOMAS

Tuberculomas are spherical, granulomatous masses thought to arise when tubercles in the brain parenchyma enlarge without rupturing into the subarachnoid space. They often occur in the absence of TBM but may be found along with TBM. Size varies 2–8 cm in diameter. It may contain necrotic caseous material and tuberculous bacilli inside. Surrounding brain parenchyma is compressed and shows edema and gliosis. In developing countries children and young adults are commonly affected. Clinical presentation depends on the site and size of the tuberculoma. In children infratentorial tuberculomas are more common. Supratentorial tuberculomas present with fever, headache, vomiting, seizures, focal neurological deficit and papilledema. Infratentorial tuberculomas present with cerebellar signs, multiple cranial nerve palsies and brainstem syndromes.

CT findings are a low or high density rounded or lobulated mass and show intense, homogeneous or ring enhancement with contrast. Wall is irregular with perilesional edema. Target sign if present is considered as pathognomonic of tuberculoma **(Fig. 2)**. This is a central calcification or nidus surrounded by a ring that enhances on contrast administration. On CT scan, tuberculomas are often confused with neurocysticercosis (NCC). Inflammatory granuloma size more than 20 mm, irregular outline, marked perilesional edema leading to midline shift and presence of focal neurological deficits are the features of tuberculomas, which can differentiate a tuberculoma from NCC.

On MRI, a non-caseating granuloma is hypointense on T1 weighted image, hyperintense on T2 weighted image and homogeneously enhancing on contrast administration. A caseating granuloma is hypointense or isointense on both T1 and T2 weighted images and ring enhancement is found on contrast administration. Variable degree of perilesional edema is found. In case of central liquefaction, center is hypointense on T1 and hyperintense on T2 weighted images with a surrounding hypointense ring. Ring enhancement is found on contrast administration. MR spectroscopy may help in diagnosis of tuberculoma as it shows a lipid peak.

Mostly diagnosis is made by radioimaging, but a stereotactic diagnostic biopsy can help in establishing accurate diagnosis.

Figure 2 Tuberculoma in left middle cerebellar peduncle near the 4th ventricle

SPINAL TUBERCULOSIS

Pott's Spine and Pott's Paraplegia

It occurs because of tuberculous infection of vertebral bodies and found in less than 1% patients of TB. Thoracic region is most commonly involved (65%) and lumbar (20%), cervical (10%), thoracolumbar (5%) and rarely atlantoaxial region may be involved. Infection of vertebral bodies starts from the bone adjacent to an intervertebral disc or sub periostium anteriorly. Subsequently collapse of vertebral body along with anterior wedging and paraspinal abscess formation occur. Paraspinal abscess leads to compression of the spinal cord. Sometimes neurological deficits are because of dural invasion by the granulation tissue **(Fig. 3)**, or compression by the debris of sequestrated bone, a destroyed intervertebral disc or dislocated vertebra. Rarely cause can be vascular due to anterior spinal artery involvement.

Disease is more common in males and young persons. Subacute, progressive sometimes acute, sensory motor paraparesis is found in 27–47% patients at presentation. Locally there is pain and tenderness over involved spine. There may be bony deformity like gibbus formation and a palpable paraspinal abscess.

Spinal X-rays are usually adequate to show vertebral bodies destruction and reduced intervertebral disc spaces. Other investigations like MRI, CT scan, myelography are often required to decide level and extent of bony involvement, paravertebral abscess and cord compression. CT-guided needle biopsy should be done if required to rule out other etiology. Majority of cases with Pott's paraplegia require surgical decompression along with ATT. Treated cases of Pott's spine may develop paraparesis later on also because of stretching of the spinal cord by a deformed canal.

Nonosseous Spinal Cord Tuberculoma

A review of 74 cases of nonosseous tuberculous paraplegia revealed that extramedullary tuberculomas were the cause in 64%, arachnoid lesion without dural involvement in 8%, and extradural-extramedullary lesions in 8% of cases. Intramedullary tuberculomas are rare. Clinical features resemble extramedullary or intramedullary tumor. Tuberculoma may be found at more than one site. MRI is the investigation of choice for these lesions.

Spinal Tuberculous Meningitis

Spinal TBM may develop when Rich's focus ruptures into the spinal arachnoid space rather than the basal meninges. It can present

Figure 3 Kyphosis due to collapse of D9–D10 vertebra with epidural granulation tissue causing cord compression

acutely or in a chronic form. Fever, headache, and radiating root pain accompanied by myelopathy are the features of acute form. Chronic variety is usually localized to a few segments and presents with progressive spinal cord compression. On examination patchy upper motor neuron and lower motor neuron signs are found. MRI shows CSF loculation and obliteration of the spinal sub arachnoid space with loss of outline of spinal cord in the cervicothoracic region and matted nerve roots in the lumbar region. It gives an appearance of *burnt candle*. There may be associated syrinx formation.

Tuberculous Radiculomyelopathy

It is also known as tuberculous arachnoiditis. Spinal cord and nerve roots are surrounded by the inflammatory exudates but not infiltrated by exudates. Neuronal injury occurs by direct compression and ischemia caused by small vessels involvement with periarteritis. Involvement can be focal, multifocal or diffuse. Clinical features of involvement of spinal cord or nerve root or both may be present. Myelography shows characteristic findings in the form of poor flow of contrast material with multiple irregular filling defects, cyst formation and sometimes spinal block. CSF findings are similar to a case of chronic meningitis, occasionally a dry lumbar tap.

Antitubercular drugs with steroid are the treatment. Surgery is required in case of medical treatment failure.

PREVENTION OF CNS TUBERCULOSIS

Although BCG vaccination and INH prophylaxis have a preventive role, an improved tuberculosis control worldwide would be more effective. Protective efficacy of BCG was not measured by any controlled trial and debate surrounding the efficacy of BCG vaccine has been ongoing since it was first developed. BCG does not provide complete protection and all forms of tuberculosis can occur in BCG vaccinated children. BCG efficacy is around 60–80% in protecting against TBM as found in various studies. Two recent meta-analyses also concluded that BCG vaccination protects against TBM. BCG-vaccinated children who do develop TBM have a milder clinical course and better short-term outcomes than do their unvaccinated counterparts. This could be attributable to a better immunological response induced by BCG vaccination. Prompt treatment of adult tuberculosis cases and INH prophylaxis is crucial in reducing incidence of childhood tuberculosis including CNS tuberculosis.

IN A NUTSHELL

1. CNS tuberculosis continues to be an important cause of neurologic handicap in developing countries.
2. Early diagnosis is difficult because of nonspecific symptoms in TBM.
3. Current laboratory diagnostic tests lack sensitivity to diagnose TBM.
4. Corticosteroids reduce risk of neurodisability and death in HIV-uninfected children.
5. Treatment of tuberculous hydrocephalus depends on the level of the cerebrospinal fluid obstruction.
6. Early diagnosis and treatment of TBM is the single most important factor determining outcome.

MORE ON THIS TOPIC

Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. Health Technol Assess. 2013;17:371-2.

Kumar R, Dwivedi A, Kumar P, Kohli N. Tuberculous meningitis in BCG vaccinated and unvaccinated children. J Neurol Neurosurg Psychiatry. 2005;76:1550-4.

Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. Arch Dis Child.1999;81:221-4.

Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 2010;10:803-12.

Nussbaum ES, Rockswold GL, Bergman TA, et al. Spinal tuberculosis: a diagnostic and management challenge. J Neurosurg.1995;83:243-7.

Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008;1:CD002244.

Thwaites GE. Advances in the diagnosis and treatment of tuberculous meningitis. Curr Opin Neurol. 2013;26:295-300.

Thwaites GE, Hien TT. Tuberculous meningitis: many questions, too few answers. Lancet Neurol. 2005;4:160-70.

van Toorn R, Solomons R. Update on the diagnosis and management of tuberculous meningitis in children. Semin Pediatr Neurol. 2014;21:12-8.

Chapter 42.17
Viral Encephalitis
Mary Iype

Encephalitis is an inflammation of the brain, and the most common etiology of encephalitis is viral infection. There are many viruses identified as the causative organism. Some cause epidemics, some are sporadic infections and a few are endemic to certain regions. In the developing world, vector breeding is facilitated due to poor environmental hygiene; and this, concurrent with the poor host immunity and vaccination coverage, make encephalitis a significant public health issue.

EPIDEMIOLOGY

The incidence of encephalitis for tropical countries ranges from 1.77 to 6.34 per 100,000 and for Western countries, the incidence is 0.5 to 7.4 per 100,000. The incidence of herpes simplex encephalitis (HSE) is 0.2–0.4 per 100,000; and accounts for 5–10% of all encephalitis. Another important causative organism of encephalitis in India is *Japanese B encephalitis (JE) virus.* Some outbreaks of encephalitis in India include enteroviruses (EV) 89, 76 in east Uttar Pradesh in 2006; EV 71 in Lucknow in 2008; Sporadic EV 71 (2004–2006) in Uttar Pradesh and the epidemic of EV 71 in 2007 in Delhi. There were outbreaks of Chandipura virus in Andhra Pradesh in 2003; in Gujarat in 2004; in Nagpur in 2005 and 2007 and sporadic cases from 2005 to 2006 in Andhra Pradesh. Nipah virus encephalitis epidemics were reported in 2001 and 2007 from West Bengal.

ETIOLOGY

Viruses that cause encephalitis include herpes simplex virus (HSV) types 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV) types 6 and 7, Coxsackie viruses, Echoviruses, EV 70 and 71, Parechovirus, Poliovirus, measles virus, mumps virus, human immunodeficiency virus (HIV), influenza viruses, Adenovirus, Parvovirus, lymphocytic choriomeningitis virus, Rubella virus, West Nile virus, La Crosse virus, St Louis virus, Powassan encephalitis virus, Venezuelan, Eastern and Western equine encephalitis viruses, Colorado tick fever virus, Dengue virus, Rabies virus, Louping ill virus, Rift Valley fever virus, Crimean-Congo hemorrhagic fever virus, Chikungunya, Murray Valley encephalitis virus and Japanese encephalitis virus.

The viruses that are common in Asia are Japanese encephalitis virus, West Nile virus, Dengue virus, Murray Valley encephalitis, Rabies virus, Chikungunya virus, Nipah virus, Kyasanur Forest disease virus, Chandipura virus, EV, Herpes, measles, mumps, VZV, and EBVs.

PATHOGENESIS

Viruses access the central nervous system (CNS) by either the neuronal or hematogenous route. The latter is most common and in arthropod-borne infections is associated with alterations of the blood-brain barrier. Access to CNS by the intraneuronal route occurs typically in rabies where the virus reaches the limbic system by traveling along the nerves, and in HSV infections. Rabies virus may reach the brain by inhalation when a person enters a cave infested with infected bats or inhalation from aerosols in the laboratory. Following the bite, the Rabies virus which has an affinity for nicotinic receptors invades the muscle. It is not known for certain whether the virus invades the muscle spindles or the motor end plates; or whether the superficial sensory nerve endings are invaded. The virus travels by retrograde axoplasmic flow to reach the cell body of the nerve invaded. Once in the CNS, the gray matter is first invaded.

Enteroviruses spread by the fecal oral route and first replicate in the Peyer's patches in the intestine. In acute viral encephalitis, a remarkable pathological finding is the infiltration of mononuclear inflammatory cells in the Virchow-Robin spaces and in the meninges around the wall of vessels (perivascular cuffing). With further disease progression, astrocytosis proliferation and hypertrophy of microglial cells with formation of microglial aggregates (microglial nodules) and neuronophagia (clusters of microglial cells surrounding a dead neuron) become prominent histopathological findings.

HHV-6, has two variants, A and B. Both of them are neurotropic in vivo and reside latently in macrophages; complicating attempts to link HHV-6 to neurological disease. However, HHV-6 is considered a possible cause of encephalitis in immunosuppressed children. EBV remains latent in B lymphocytes, the exact mechanism of activation of the Epstein-Barr viral genome resulting in encephalitis is controversial.

Herpes simplex encephalitis Unlike other viral encephalitis, there is no viremia. The virus traverses mucous membranes and then travels by retrograde axonal transport to the trigeminal ganglion, where it remains dormant. There is periodic activation and anterograde axonal transport to allow viral shedding and infection of new hosts. Spread through the olfactory nerve endings is also postulated.

Japanese B encephalitis Soon after the mosquito inoculates a patient, there is viral multiplication in the skin; this results in viremia and later invasion of the nervous system. The exact mechanism of penetration of the brain is unknown.

CLINICAL FEATURES

Encephalitis or another CNS infection should be suspected in a child with fever, altered behavior or consciousness, new onset seizures, or neurological deficits. Inflammatory demyelinating diseases like acute disseminated encephalomyelitis, acute renal failure, hepatic failure, intoxication with drugs or poisons, Reye syndrome, autoimmune encephalitis, and cortical venous thrombosis may be considered as differential diagnoses depending upon the clinical scenario. The onset of the illness, any other associated medical illness, telltale evidence of other illness like an odor, rashes or signs of trauma should be picked up. The constellation of presenting symptoms, the course of illness and the findings on examination should be analyzed systematically to arrive at a diagnosis and to plan investigations.

If the patient with encephalitis has concomitant myocarditis, pleurodynia, herpangina or hemorrhagic conjunctivitis an enterovirus should be suspected. Signs of hemorrhage may also be seen with Dengue virus, Yellow fever virus and Rift Valley fever virus.

Children with JE are known to present with mutism. Tremor and other involuntary movements are noted with fever. Fever abates in 2–3 weeks when the involuntary movements become more obvious and occur in the form of choreoathetosis or ballism.

Presence of movement disorders, orofacial dyskinesias, seizures that are resistant to treatment and a subacute onset should point to an autoimmune encephalitis and the appropriate investigations should be planned. **Table 1** shows the possible etiologic agent based on the clinical presentation.

If the patient who presented with an acute encephalitic syndrome shows features of neuritis or myeloneuritis, EBV should be entertained as a possible etiological agent. Ophthalmoplegia, autonomic and sensory neuropathy are seen in EBV encephalitis. Subacute encephalitis may be seen in CMV encephalitis.

Measles can present with four different encephalitic pictures: acute encephalitis, postviral encephalomyelitis, measles inclusion

Table 1 Possible viral etiological agents based on clinical presentation

Clinical presentation	Possible etiological agent
Cerebellar ataxia	Varicella zoster virus
Dementia	HIV, measles virus
Poliomyelitis-like flaccid paralysis	Japanese B virus, poliovirus, enteroviruses, West Nile virus, tick-borne encephalitis virus
Extrapyramidal manifestations	Japanese B virus, West Nile virus, Nipah virus
Retinitis	CMV, West Nile virus
Rash	VZV, HHV-6, rubella virus, measles virus, hand foot and mouth disease
Diarrhea	Enterovirus
Respiratory tract findings	H1N1 and other influenza viruses, adenovirus
Parotitis	Mumps virus
Lymphadenopathy	HIV, EBV, CMV, measles virus, rubella virus

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpes virus; VZV, varicella zoster virus.

BOX 1 Differential diagnosis of viral encephalitis

- Autoimmune encephalitis
- Sjögren syndrome
- Hashimoto's thyroiditis
- Systemic lupus erythematosus
- Acute disseminated encephalomyelitis
- Vasculitis of CNS
- Bulbar variant of Guillain-Barré syndrome
- Primary and metastatic brain tumors
- Metabolic and toxic diseases
- Nonconvulsive status
- Reye syndrome.

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body encephalitis, and subacute sclerosing panencephalitis (SSPE). Acute encephalitis presents with fever, rash, cough, coryza, and Koplik spots. Cerebrospinal fluid (CSF) shows pleocytosis and EEG usually shows nonspecific slowing. Postviral encephalomyelitis refers to a demyelinating illness occurring within 2 weeks of the rash and consists of altered mental status, seizures, and focal neurological deficits. Measles inclusion body encephalitis presents with dementia, behavioral abnormalities, myoclonus, seizures and even coma. Death occurs in a few weeks after onset. SSPE is a rare late complication of measles presenting with decreasing school performance, behavioral abnormalities and a characteristic slow myoclonus. Gradually there will be affection of the pyramidal and extrapyramidal tracts with macular pigmentary degeneration.

Rabies encephalitis often has to be distinguished from demyelination after rabies vaccine given as postexposure prophylaxis. The features that help one to distinguish rabies encephalitis from postvaccinial demyelination would include presence of hydrophobia or/and aerophobia, autonomic features like salivation, and rapid progression which favor rabies. MRI of the brain shows grey matter affection as opposed to predominantly white matter affection in postvaccinial demyelination.

A careful search should be made for the skin lesions of dengue, chikungunya, herpes zoster and hand foot and mouth disease. HHV-6 normally causes roseola. Hypertension in the child with altered sensorium would open up another set of diagnoses to pursue. The investigations should be tailored according to the patient's clinical history and presentation.

DIFFERENTIAL DIAGNOSIS

It is imperative to keep in mind that all the children with altered sensorium do not have viral encephalitis and that there are other treatable differential diagnoses. **Box 1** shows the possible differential diagnoses of viral encephalitis. Vasculitis involving the nervous system, brain tumors, demyelinating disease, autoimmune encephalitis, Hashimoto's encephalitis, metabolic and toxic encephalopathies and hypoxic brain damage should be considered, as the clinical picture warrants.

INVESTIGATIONS

Lumbar puncture (LP) should be done in all cases unless it is contraindicated. When LP is contraindicated due to raised

intracranial pressure (ICP), a CT scan should be performed as soon as possible with a plan to do a subsequent LP if the imaging does not reveal significant brain shift. In cases where LP is deferred, the case should be repeatedly reviewed and LP should be done when deemed safe.

Cerebrospinal fluid should be examined for cytology, biochemistry, Gram stain, Ziehl-Neelsen stain for acid-fast bacilli, bacterial culture, latex agglutination, polymerase chain reaction (PCR) for HSV-1 and -2, and IgM antibodies for JE and for Dengue virus (if suspected) **(Table 2)**. CSF should be checked for the total and differential cell count, Gram stain and acid-fast bacilli stain and subjected to culture and sensitivity testing. A sample should be retained for future investigational needs.

In 10%, the white cell count of the CSF will be normal. The CSF may show pleocytosis with raised protein in all encephalitis including rabies. Ideally viral culture from CSF, brain tissue, throat and stool specimens is necessary to identify the pathogen; but as these facilities are not commonly available, isolation of the viral nucleic acid from CSF is taken as diagnostic. CSF PCR tests are available for herpes viruses, EV and Parechovirus. The result of the PCR test for nucleic acid depends on the window during which the CSF was collected; with the highest yield during the first week and less during the second and subsequent weeks. Multiplex PCR is preferred over single PCR. Microarray for the viral DNA is expensive and not easily available.

If PCR of the CSF was not already done, or if CSF PCR is negative, CSF HSV specific IgG antibody testing should be done 2 weeks after onset of illness. When CSF PCR is negative, the serum has to be checked for IgM antibodies in two samples 2–3 weeks, apart for HSV-1 and -2, CMV, VZV, HHV-6, Enterovirus, Parvovirus, Adenovirus and Influenza A and B virus infection.

Antigen detection can be attempted from throat samples using immunofluorescence and enzyme linked immunosorbent assay; this will help detect HSV, VZV, influenza A and B and parainfluenza viruses. Virus type can be identified from cell cultures by electron microscopy.

If the patient has psychiatric symptoms, intractable seizures and new onset movement disorders with coma or if the patient has telltale evidence of an ongoing malignancy; antibodies to N-methyl-D-aspartate receptor and voltage-gated potassium channels should be checked. If the child with encephalitis has associated atypical pneumonia, *Mycoplasma* and *Chlamydia* serology and cold agglutinins in serum should be sought.

In cases of suspected AIDS virus encephalitis, HIV antibody test is done. In the immunocompromised, the CSF is subjected to India ink stain for *Cryptococcus* and Ziehl-Neelsen stain for *Mycobacterium tuberculosis*. Diagnostic investigations for immunocompromised patients with altered consciousness are given in **Box 2**. Throat swabs should be sent for H1N1 in case of clinical suspicion. In appropriate cases, throat and rectal swabs for enterovirus should be sent.

Table 2 The diagnostic modality of choice for each virus

Virus	Test of choice
Japanese encephalitis virus	Virus-specific IgM antibody in a single sample of CSF or serum, as detected by an IgM-capture ELISA specifically for Japanese encephalitis virus
Enteroviral encephalitis	Detection of EV genome by RT-PCR or an equally sensitive and specific nucleic acid amplification test (real time) in CSF. Isolation of virus from serum/stool/throat swab
Dengue viral encephalitis	Dengue virus-specific IgM antibody in a single sample of CSF as detected by an IgM-capture ELISA
HSV encephalitis	Detection of HSV DNA in CSF by PCR HSV specific antibody titers in serum and CSF
Mumps virus encephalitis	Detection of mumps virus RNA in CSF by PCR
Varicella zoster virus encephalitis	Detection of VZV DNA by PCR in CSF
Nipah virus	Detection of Nipah virus specific IgM antibodies in serum and CSF by IgM-capture ELISA PCR from CSF
Measles virus	Appearance of measles virus specific IgM antibody in the CSF
Chandipura virus	Detection of specific IgM antibodies in CSF by ELISA
Rabies virus	Corneal imprint smear, Nuchal biopsy, PCR for Rabies virus in CSF

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HSV, herpes simplex virus; PCR, polymerase chain reaction.

BOX 2 Investigations in immunocompromised patients with altered consciousness

- CSF PCR for HSV-1 and -2, VZV, enteroviruses, EBV, CMV, HHV-6 and -7, Adenovirus, Influenza and Parvovirus B_{19}
- CSF AFB staining and culture for Mycobacterium tuberculosis
- CSF culture for *Listeria monocytogenes*
- Blood culture
- Indian ink staining and cryptococcal antigen testing in CSF
- Antibody testing and if positive CSF PCR for *Toxoplasma gondii*
- Antibody testing of serum and if positive CSF for syphilis

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpes virus; VZV, varicella zoster virus.

Magnetic Resonance Imaging

Magnetic resonance imaging (including diffusion weighted imaging should be done in all patients, ideally within 24 hours if not within 48 hours). **Table 3** lists the MRI changes that act as pointers to the etiologic agent. Magnetic resonance spectroscopy, positron emission tomography and single-photon emission computed tomography are not indicated in suspected viral encephalitis.

Electroencephalography

Electroencephalography has limited utility in the evaluation of a child with acute viral encephalitis; especially with the recognition that periodic lateralized epileptiform discharges (PLEDS) are not diagnostic or exclusive to viral encephalitis. PLEDS are sharp waves or slow sharp waves that are seen recurring every 1–4 sec. However, it should be kept in mind that an EEG would be valuable in the evaluation; especially to pick-up nonconvulsive status that needs management, to pick-up a metabolic encephalopathy misdiagnosed as viral encephalitis and to exclude psychiatric causes of altered sensorium. EEG may show focal slowing or spiking; diffuse slowing follows, with a temporal predominance.

Stereotactic Brain Biopsy

Stereotactic brain biopsy may be considered in cases where no diagnosis has been reached and if the patient is deteriorating. If there is no focal lesion, the biopsy is taken from the nondominant frontal lobe. An experienced neurosurgeon and an experienced histopathologist are prerequisites for a brain biopsy. Characteristic owl-eyed inclusions are described in the cytoplasm of neurons in CMV encephalitis. Nuchal pad biopsy is the standard procedure in suspected rabies.

When the etiology is not clear, other microbiological investigations must be obtained. These are also required in epidemic situations, where the etiology has not been established. The local health authorities must be informed, and a microbiologist should be consulted when taking the samples. These samples include urine, throat swab, nasopharyngeal aspirate, serum (acute, and convalescent after 2 weeks) and swab from vesicles or rash, if present.

Table 3 MRI changes that could point to the etiologic agent in children with viral encephalitis

Region showing changes	Possible etiology
• Frontotemporal hyperintensities/significant edema and hemorrhage in the temporal lobes	HSV encephalitis
• Hippocampal	Limbic encephalitis due to VGKC antibodies
• Mixed intensity or hypointense lesions on T1WI and hyperintense or mixed intensity lesions on T2WI predominantly in the thalami, but also in the basal ganglia, brainstem, cerebellum, and cortical areas	Some arboviral encephalitis like Japanese B encephalitis
• Corpus callosum	H1N1 virus
• Diffuse excessive high-signal intensity and multiple punctate lesions in the white matter of periventricular region	Parechovirus, Nipah virus
• Hyperintense lesions on T2WI located within the brainstem (midbrain, pons and medulla) and dentate nuclei of the cerebellum. High-signal lesions can also be found in the anterior horn cells of spinal cord in patients with acute flaccid paralysis	Enterovirus 71
• Abnormalities in deep gray matter and brainstem (50%); white matter lesions mimicking demyelination	West Nile virus
• Symmetrical thalamic and basal ganglia changes	Rabies virus

Abbreviations: HSV, herpes simplex virus; VGKC, voltage-gated potassium channels.

MANAGEMENT

Every case of suspected viral encephalitis should be notified to the appropriate government agency to initiate case surveillance and the diagnostic process. Supportive care assumes great importance in the management of viral encephalitis with immediate attention to the airway, breathing and circulation. Hyperthermia and hypothermia should be corrected. Management of raised ICP when present with head elevation to 15–30°, use of intravenous mannitol, diuretics and controlled hyperventilation are part of the successful management. Euglycemia and electrolyte balance should be maintained. Seizures should be managed with timely recognition and treatment of nonconvulsive seizures. Ventilatory support, oxygenation and management of shock and syndrome of inappropriate antidiuretic hormone secretion should be instituted whenever necessary.

In areas endemic for malaria, empirical treatment for the same is started until a definite other diagnosis is established or malaria is ruled out. Empirical treatment for bacterial meningitis should be instituted in all cases. Doxycycline should also be initiated if the chances for a rickettsial or ehrlichial infection are high. Intravenous macrolides are included in the regime if there is suspicion of *Mycoplasma pneumoniae* encephalitis.

Empirical treatment with intravenous acyclovir (10 mg/kg three times daily or) 500 mg/m^2 8 hourly should be started if the initial CSF and/or imaging findings suggest viral encephalitis, or within 6 hours of admission if viral encephalitis cannot be ruled out with the available investigations and the patient shows no signs of recovery. Once the diagnosis of HSV encephalitis is proved, intravenous acyclovir treatment should be continued for 14–21 days. A repeat LP should be done at 21 days to confirm that the CSF is negative for HSV by PCR; if the CSF is still positive, acyclovir should be continued intravenously and PCR repeated until it is negative.

In patients who are HSV PCR negative, acyclovir can be stopped in immunocompetent patients, if (1) an alternative diagnosis has been made, (2) If HSV PCR in the CSF is negative on two occasions 24–48 hours apart, and MRI is not characteristic for HSV encephalitis, (3) HSV PCR in the CSF is negative once greater than 72 hours after neurological symptom onset, with unaltered consciousness, normal MRI (performed >72 hours after symptom onset), and a CSF white cell count of less than 5/mm^3.

Corticosteroids do not have a role in the treatment of viral encephalitis. Acyclovir 10–15 mg/kg three times daily for 3 weeks intravenously is recommended, with or without a short course of steroids for VZV encephalitis. No specific treatment is needed for cerebellitis due to VZV.

Ganciclovir (5 mg/kg intravenously twice daily) with foscarnet (60 mg/kg every 8 hours or 90 mg/kg intravenously every 12 hours) is recommended as initial therapy in CMV encephalitis; followed by ganciclovir (5 mg/kg/day) or foscarnet (60–120 mg/kg/day) for 3 weeks and 6 weeks for immunosuppressed patients. Oseltamivir is indicated in influenza virus encephalitis. Ribavirin has been used with success in acute measles virus encephalitis. There is experimental evidence of benefit of minocycline in JE.

PROGNOSIS

In general, prognosis is poorer in infants younger than 1 year. Rabies encephalitis is progressive and fatal, and therapy is largely palliative. The mortality rate in the case of measles encephalitis is between 10% and 20%, while sequelae are observed in 20–40% of patients who recover. Untreated, HSE is fatal in 70%. 30% die at 3 months with treatment. With acyclovir treatment less than half survive with no sequelae. Only 2.5% regain absolutely normal brain function. The good prognostic features include, short duration illness, and better sensorium when treatment was initiated. Even with early treatment, nearly two-thirds of the survivors may have significant neurologic sequelae. In animal models, seizures were associated with long-term mortality and, therefore, seizure control is emphasized in the management. Children who were

afflicted with encephalitis due to any virus could end up with a postencephalitic syndrome consisting of behavioral abnormalities, cognitive impairment and seizures.

REHABILITATION

Prompt recognition and management of respiratory infection, ventilator-associated pneumonia and urinary tract infection is necessary for recovery. Nutrition of the child should be supervised; the feeding tube, urinary catheter and tracheostomy should be tended carefully. The posture of the patient should be optimum to prevent contractures. Sessions with the psychologist, physiotherapist, occupational and speech therapist should be begun early.

PREVENTION

Japanese B encephalitis is the leading form of viral encephalitis in Asia, with a high mortality especially in children. Incomplete surveillance in many affected areas gives a false idea about the mortality. The WHO has, therefore, given priority for the prevention of JE and has initiated JE surveillance. Syndromic surveillance is undertaken for JE. In order to ensure that no case is missed, it is mandatory to report cases of acute encephalitic syndrome. Details are available in the chapter on *Japanese Encephalitis* in Section 31.

IN A NUTSHELL

1. Children with suspected viral encephalitis are often inadequately investigated and managed.
2. MRI or CT is a mandatory part of the diagnostic armamentarium in patients with encephalitis. PCR testing for the etiologic agent should be attempted. In doubtful cases, the stored serum and CSF samples should be available for serological testing.
3. Supportive therapy is still the mainstay.
4. Treatable differential diagnoses should always be considered during the evaluation of a patient with acute encephalitis syndrome.
5. Acyclovir should be given empirically to all suspected encephalitis. If bacterial meningitis cannot be ruled out or until it is ruled out, patient should receive treatment for pyogenic meningitis. In case of suspicion of rickettsial or ehrlichial infection, doxycycline should be given.
6. Once an etiologic agent of encephalitis is identified, antimicrobial therapy should be targeted to that infectious agent, or therapy should be discontinued if treatment directed against the etiologic agent is not available.

MORE ON THIS TOPIC

Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008;65:596-600.

Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system. Nature Clin Prac Neurol. 2007;3:82-94.

Gonzalez-Rabelino GA, Fons C, Rey A, et al. Craniectomy in herpetic encephalitis. Pediatr Neurol. 2008;39:201-3.

Kamei S, Sekizawa T, Shiota H, et al. Evaluation of combination therapy using acyclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatr. 2005;76:1544-9.

Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children—Association of British Neurologists and British Pediatric Allergy Immunology and Infection Group National Guidelines. J Infect. 2012;64:449-77.

Kumar A, Shukla D, Kumar R, et al. An epidemic of encephalitis associated with human enterovirus B in Uttar Pradesh, India, 2008. J Clin Virol. 2011;51:142-5.

Sejvar JJ. The evolving epidemiology of viral encephalitis. Curr Opin Neurol. 2006;19:350-7.

Sharma S, Mishra D, Aneja S, Kumar R, et al. Consensus guidelines on evaluation and management of suspected acute viral encephalitis in children in India. Indian Pediatr. 2012;49:897-910.

Steiner I, Budka H, Chaudhuri A, et al. Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2005;12:331-43.

Chapter 42.18
Neurocysticercosis
Pratibha Singhi

Neurocysticercosis (NCC) is a parasitic infection of human brain caused by encysted larvae—cysticercus of the pork tapeworm *Taenia solium*. According to a recent meta-analysis epilepsy is associated with NCC in over a quarter of patients in endemic regions. Pediatricians in developing countries must have a high index of suspicion and should be aware of the varied manifestation of NCC as early diagnosis and treatment is highly rewarding.

EPIDEMIOLOGY

Approximately half a billion population worldwide is estimated to have cysticercosis. NCC is endemic in Southeast Asia, Latin America and sub-Saharan Africa, especially in the pig-rearing or pork-eating economically deprived communities. Global prevalence is difficult to assess as blood investigations are often noncontributory and neuroimaging is required to establish the diagnosis. A population-based study from Mexico, in 154 apparently asymptomatic residents using head CT scan for detection of NCC, reported a prevalence of 9.1%. In children (0–19 years), the estimated prevalence was 13.2%. In rural parts of North India, 25% cases with seizures were found to have an active NCC and another 10% a calcified granuloma. NCC contributes to a third of epilepsy cases in Latin America and 30–50% of acquired epilepsy cases in sub-Saharan Africa. Approximately 50% of children with focal seizures have been shown to have NCC in hospital-based studies from Peru and North India. The high prevalence of NCC in the poorest of poor leads to large economic losses in the already resource constrained developing world. Global spread of the disease has occurred with frequent international travel. Cysticercosis is now increasingly being reported from the developed world. Around 1,320–5,050 new cases of NCC occur every year in USA.

LIFE CYCLE OF *TAENIA SOLIUM*

Humans are the definitive host of adult *T. solium*. They acquire it by ingesting undercooked pork containing cysticerci. Once ingested, the cysts release larvae that attach to intestinal mucosa via their scolices and mature into adult worms. The adult female worm releases proglottids (segments) heavily laden with eggs that are passed in the stool of the carrier human. These eggs are later ingested by pigs grazing on soil contaminated by human excreta. The eggs release larvae in the pig intestine to form larvae that traverse the intestinal mucosa and spread through the blood stream to the pigs' muscles to form cysts; the cycle of *T. solium* is thus completed. Rate of transmission is high in rural communities where pigs roam free and open defecation is rampant.

Neurocysticercosis is caused by accidental human ingestion of *T. solium* eggs shed in stool of human tapeworm carriers. After entering the human gut, *T. solium* embryos (oncospheres) hatch in the small intestine and the larvae invade the bowel mucosa and disseminate hematogenously to brain, liver, striated muscle, subcutaneous tissue and eyes. They lodge at these sites and within 3 weeks to 2 months form tissue cysticerci which are fluid-filled membranous cysts with invaginated scolex. Cysticerci that reach the brain cause neurocysticercosis.

It is a common misconception that cysticercosis occurs because of eating pork. Pork ingestion leads to exposure to *T. solium* larvae which mature into adult tapeworms and cause taeniasis and not cysticercosis. Cysticercosis is transmitted through food contaminated with *T. solium* eggs either through food handlers who are carriers or through contaminated soil. An asymptomatic household tapeworm carrier is the most common source of infective eggs.

PATHOGENESIS

Within the brain, cysticerci are mostly located at the gray-white matter interface. These cysts may survive for prolonged periods without evoking host immune responses due to a number of protective mechanisms. Experimental models suggest that the live parasite releases a variety of substances such as taeniaestatin, glycoconjugates, paramyosin and secretory proteases which suppress the host immune reaction against the foreign cyst. The favorable environment withers and an inflammatory response is generated once the parasite is dead. It has been suggested that downregulation of cytokines through alternately activated macrophages may be another immune protective mechanism. The host immune attack causes cyst lysis and appearance of edema that is seen as mass effect and contrast enhancement on neuroimaging. In most cases, previously asymptomatic cysts become symptomatic at this stage of active inflammation and result in myriad forms of neurological signs and symptoms depending on their location, especially seizures, headache, and vomiting.

The brain parenchymal cyst evolves through four stages. The cyst characteristics and radiological appearance is provided in **Table 1**. Ultimately, the cysts either resolve or get transformed into a calcified granuloma. When calcification occurs, recurrent seizures may occur due to unclear pathogenetic mechanisms. Matrix metalloproteinases have been implicated in the pathogenesis of seizures in calcified lesions.

CLINICAL FEATURES

Neurocysticercosis is a disease with pleomorphic presentation. Its spectrum ranges from being asymptomatic to recurrent seizures and acute hydrocephalus. The clinical syndrome depends primarily upon the stage (viable/degenerating), location, size and number of cysts within the brain. Largely, NCC has two forms namely parenchymal and extraparenchymal. Classically, the parenchymal form is commoner and presents with seizures in children in contrast to the rarer extraparenchymal form that usually presents with acutely raised intracranial pressure (ICP). Major differences between the two forms are highlighted in **Table 2**. Pediatricians, however, must remember that the two forms may simultaneously or sequentially present in a single patient. Also, all stages of cysticercal cysts from vesicular to calcified granuloma may be seen in the same patient simultaneously.

Parenchymal Neurocysticercosis

This is the most common form of NCC in children as well as adults. The clinical feature depends upon whether a single or multiple cysts exist in the brain parenchyma. A single ring-enhancing lesion on contrast-enhanced CT scan of head **(Fig. 1)** is the most common finding in Southeast Asian countries. Clinical studies from endemic regions suggest that most of the parenchymal cysts are asymptomatic or are either found incidentally or are never diagnosed. Children may remain asymptomatic for several months or years until they present with an episode of afebrile seizure. In a series of 500 patients from our center, 95% had seizure as a presenting complaint. Seizures are short-lasting (less than 5 minutes) and are mostly focal (84–87%) usually complex partial seizures. Generally, a single seizure is seen. Clustering of seizures is uncommon but may occur in the initial 72 hours in up to 6% cases. Various other neurological signs and symptoms in descending order of frequency are presented in **Table 3**. Studies

Table 1 Stages of development of neurocysticercal cyst

Stages	Characteristics	Radiological features
Vesicular stage (Viable)	Live cyst filled with clear fluid, has a thin semitransparent wall, with an eccentric opaque 4–5 mm scolex. There is no evident inflammation around it and it is usually asymptomatic.	CSF density/intensity cyst with no enhancement. T1 hyperintense scolex may be visible. Wall is isodense to brain parenchyma.
Colloidal vesicular stage (Active)	Degenerating, an inflammatory response is elicited, the larva undergoes hyaline degeneration and the clear cyst fluid is replaced with opaque gelatinous material.	Cyst fluid turns turbid. *CT scan:* Hyperdense to CSF *MRI T1:* Hyperintense to CSF Cyst wall thickened and enhancing Surrounding edema present Scolex visible as an eccentric focus.
Granular nodular stage (Inactive)	Cyst contracts and the walls are replaced by focal lymphoid nodules and necrosis.	Cyst wall retracts. Edema decreases. Enhancement persists but is less marked.
Nodular calcified stage (Inactive)	The cyst transforms into a disk or nodular calcified lesion.	End-stage calcified cyst No enhancement No edema Signal drop out on T2 MRI sequences

Table 2 Differences between parenchymal and extraparenchymal neurocysticercosis (NCC)

Characteristics	Parenchymal NCC	Extraparenchymal NCC
Appearance	Small, cysts (5–20 mm). All 4 stages may be seen	Large, lobulated cysts adapting according to site of lodgment
Scolex	Easily visualized	Difficult to visualize
Clinical presentation	Seizures	Raised intracranial pressure, hydrocephalus
Imaging technique for diagnosis	CECT/CE-MRI brain	3D-CISS/FIESTA MRI sequences
Treatment	Antihelminthic therapy	Multiple course of antihelminthic therapy and surgical excision
Prognosis	Good	Poor
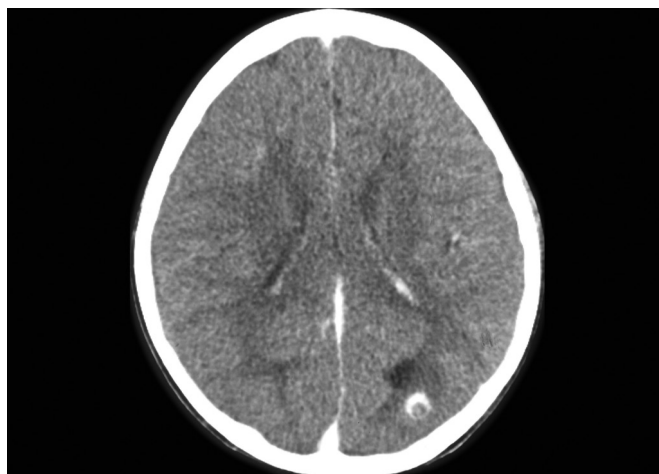
Figure 1 Contrast-enhanced computed tomography head shows single enhancing lesion with eccentric scolex and perilesional edema

Table 3 Frequency of clinical features in parenchymal neurocysticercosis in children

Features	Percentage	Features	Percentage
Seizures	70–95	Papilledema	2–7
Nausea and vomiting	25–31	Motor neurodeficit	4–6
Headache	25–28	Cranial nerve palsy	0–1
Status epilepticus	2–32		

Adapted from Baranwal et al, 1998; Singhi et al, 2000; Talukdar et al, 2002

have shown some regional differences in the clinical presentation of NCC across the world. In India and other Asian countries, NCC almost always is symptomatic in the degenerating stage in contrast to a sizeable proportion of cases from Latin America where viable vesicular cysts are seen in symptomatic patients.

In children with large number of parenchymal cysts, an intense immune reaction develops resulting in diffuse brain edema and a clinical scenario termed cysticercal encephalitis. The patients present with altered sensorium, headache, seizures, status epilepticus, visual blurring or other signs of raised ICP. Cysticercal encephalitis is associated with poorer prognosis when compared to single parenchymal NCC.

Other rare presentations of NCC include isolated cranial nerve palsy, ptosis, intranuclear ophthalmoplegia and dorsal midbrain syndrome due to brainstem NCC, movement disorder (basal ganglia NCC), meningitis, behavioral and psychiatric manifestations.

Extraparenchymal Neurocysticercosis

Extraparenchymal NCC may result from intraventricular or subarachnoid cysticerci. Rarely, it may present as spinal or ocular disease.

Intraventricular Neurocysticercosis

Cysticerci may be present inside the ventricular system as free-floating cysts or attached to the ependyma. The child becomes

symptomatic whenever the cerebrospinal fluid (CSF) outflow is blocked due to an enlarging cyst or obstruction of ventricular foramina. The most preferred locations within the ventricular system are fourth ventricle (53%), third ventricle (27%), lateral ventricles (11%) and aqueduct (9%). Children may present with acute raised ICP or obstructive hydrocephalus. The obstruction in CSF flow may occur abruptly or gradually, intermittently or permanently. Rarely, mobile cysts may cause intermittent obstruction and lead to episodic loss of consciousness with head movement—Brun's syndrome.

Subarachnoid Neurocysticercosis

Cysticerci may lodge in the subarachnoid spaces in the sylvian fissure and basal cisterns and induce inflammation giving rise to arachnoiditis often accompanied by hydrocephalus, meningitis or vasculitis. Cysts within the sylvian fissures may at times enlarge disproportionately without scolices and appear as a lobulated mass with *bunch of grapes* appearance called *racemose* NCC. These giant cysticerci may cause mass effect, hydrocephalus, secondary infarcts and focal neurological deficits.

Spinal Neurocysticercosis

Occurs rarely; signs and symptoms of spinal dysfunction may be seen such as radicular pain, paresthesias, sphincter disturbances and paraplegia when cysts lodge in the spinal subarachnoid space. Intracranial subarachnoid NCC is usually associated with spinal lesions.

Ocular Cysticercosis

Ocular cysticercosis is seen in 1–3% of cases. Cysts may reside in any part of the eyes including the subretinal space, vitreous humor, anterior chamber, conjunctiva and extraocular muscles, and cause symptoms accordingly.

APPROACH TO DIAGNOSIS

The signs and symptoms of NCC are nonspecific and, therefore, the mainstay of diagnosis is imaging. Combination of other factors such as epidemiology, symptomatology and serology may provide corroborative evidence. Diagnostic criteria based upon clinical, radiological, immunological and epidemiological data were proposed by Del Brutto in 2001 and later revised; however, they have not been validated in various parts of the world.

Neuroimaging

A reasonable clinical approach is to obtain a contrast-enhanced computed tomography (CECT) head in any child with suspected NCC. If CT is not contributory and the suspicion of NCC is high then a CE-MRI brain and serology should be considered. In most cases, CT is sufficient to establish a diagnosis except in certain cases such as intraventricular or subarachnoid NCC, cysticercal encephalitis, brainstem NCC or when scolex is not identified.

Parenchymal Neurocysticercosis

The characteristic CT finding in NCC is a small (< 20 mm), low-density smooth-walled lesion with ring or disk enhancement and an eccentric scolex appearing as a bright central dot. In the Indian subcontinent most cases present as a single enhancing lesion (SEL) representing a degenerating cyst. However, a significant proportion of cases from Latin America and Africa have multiple viable cysts at presentation. A mild-to-moderate perilesional edema is often seen **(Fig. 1)**. Infrequently, numerous cysts of varying stages are seen studded over the brain parenchyma giving rise to a *starry sky appearance* which is a hallmark of NCC. Calcified cysts, best seen on CT, are small 2–4 mm in diameter (range 1–10 mm), solid and nodular. Presence of multiple parenchymal calcifications on CT is highly suggestive of NCC. The CT findings of various stages of parenchymal cysts are tabulated in **Table 1**.

Magnetic resonance imaging (MRI) of brain is superior to CT in detecting NCC, visualizing scolex and identifying extraparenchymal cysts. The scolex is best seen on proton density-weighted images as a small 2–4 mm nodule within the cyst cavity that is isointense to hyperintense relative to white matter. The first indication of cyst degeneration is the presence of enhancement. As the degeneration progresses, the cyst content changes from hyperintense to hypointense on T2 images and the cyst wall changes from hypointense to hyperintense appearance.

Extraparenchymal Neurocysticercosis

Computed tomography (CT) may not be able to identify small intraventricular lesions; however, leptomeningeal enhancement and large racemose NCC can be identified as cystic hypodense lesions in the subarachnoid space in the sylvian fissures or cerebellopontine angle. High-resolution T2 MR sequences such as three dimensional-constructive interference in steady state (3D-CISS) and fast imaging employing steady state acquisition (FIESTA) are superior in identifying scolex in the intraventricular/subarachnoid cysts.

Serology

Serology acts an adjunctive modality to imaging in the diagnosis of NCC. Number of serological tests detecting anticysticercal antibody or cysticercal antigen in serum and CSF have been developed. In general antibody detecting techniques are preferred over assays employing unfractionated antigens. The enzyme-linked immunoelectrotransfer blot developed by CDC is highly specific (83–100%) and 100% sensitive for multiple and extraparenchymal NCC. It utilizes affinity-purified glycoprotein antigen from *T. solium* cysticerci (Tsang et al., 1989). However, like other serological tests, it lacks sensitivity for low disease burden—single NCC or calcified NCC. A comparative study from our center showed that antigen detecting ELISA and antibody detecting dot-blot assays are more sensitive for multiple lesions (100%) when compared to single lesion (87%). Serological tests do not differentiate between neural and extraneural cysticerci and therefore, false positive results can occur in endemic regions. Various newer assays based on excretory secretory antigens, synthetic polypeptides and *nano bodies* are under evaluation. A positive test result supports the diagnosis but a negative test does not exclude the diagnosis.

Cerebrospinal Fluid

Lumbar puncture is not required for the diagnosis of NCC. In parenchymal NCC, the CSF is normal. In the setting of cysticercal meningitis, encephalitis and arachnoiditis, CSF may show elevated protein, low sugars and pleocytosis. Cells may be predominantly lymphocytes, neutrophils or eosinophils. Eosinophilic meningitis usually suggests a parasitic etiology and therefore may help in differentiating from other nonparasitic causes of chronic meningitis such as tuberculosis.

Other Investigations

Peripheral eosinophilia may be seen occasionally. Stool examination may detect taeniasis but is nonconclusive for cysticercosis. Biopsy of subcutaneous nodules may detect a viable parasite and muscle radiographs may detect calcified extraneural cysticerci. Such tests are rarely required in clinical settings.

DIFFERENTIAL DIAGNOSIS

In endemic countries, NCC is generally the most common acquired cause of first episode of afebrile focal seizure in children and should be actively excluded by neuroimaging. Depending on the clinical scenario or radiological findings other differentials have to be considered. Most of endemic regions for NCC are also endemic for tuberculosis. Small tuberculoma may also present as SELs. Visualization of scolex within the cyst cavity is a pathognomic radiological finding of NCC. If the scolex cannot be identified, tuberculoma needs to be considered. Tuberculosis must always be excluded in such cases with clinical history, examination and laboratory investigations such as Mantoux, chest X-ray, and gastric aspirate analysis for acid fast bacilli. There are a number of ways of differentiating between these two most common causes of SEL **(Table 4)** but it may not always be possible. Newer MRI techniques such as CISS and FIESTA are superior to spin echo MRI in identifying scolex. Lactate peak and choline/creatine ratio greater than 1 on proton magnetic resonance spectroscopy may favor a diagnosis of tuberculoma. Other differentials of SEL are microabscesses, toxoplasmosis, mycotic granulomas and primary or metastatic tumors. Rarely, focal demyelinating lesions may also show ring enhancement. Parenchymal calcifications may be seen in intrauterine infections, metabolic disorders and vascular malformations.

Cysticercal meningitis/encephalitis has to be differentiated from other possible etiologies of chronic meningitis such as tubercular and fungal meningitis. Presence of associated parenchymal cysts and eosinophilia may favor NCC over other nonparasitic etiologies. Intraventricular cysts have to be differentiated from colloid, arachnoid, and epidermoid cysts.

MANAGEMENT

Treatment of NCC is a two-pronged approach, namely:
1. Symptomatic therapy with analgesics, anti-inflammatory agents and antiepileptics
2. Definitive cure with antihelminthic therapy for parenchymal lesions and surgical excision for extraparenchymal lesions.

Symptomatic Treatment

Symptomatic therapy is guided by the clinical presentation, location of cysts and presence of raised ICP. Children presenting with status epilepticus, altered sensorium or signs and symptoms of acutely raised ICP may require emergency admission and hospitalized care. Children with first episode of seizure, infrequent seizures or headache can be managed at home.

Table 4 Differences between parenchymal neurocysticercosis and tuberculoma

Features	Neurocysticercosis	Tuberculoma
Size	< 20 mm	> 20 mm
Site	Supratentorial (gray-white junction)	*Infratentorial
Perilesional edema	Mild	Moderate/severe
Midline shift	Less common	More common
Cyst wall	Thin, smooth	Thick, irregular, lobulated
Eccentric nodule (scolex)	Present	Absent
Raised intracranial pressure	Uncommon	Common
Progressive focal deficit	Uncommon	Common

*Usually

Antiepileptics

As seizures are the most common presenting feature, early initiation of appropriate antiepileptic drug (AED) is of utmost importance. No trial has compared the efficacy of various antiepileptics for seizures secondary to NCC. However, most cases respond well to standard doses of carbamazepine or phenytoin monotherapy. The duration of AED therapy has often been debated. Seizure recurrence correlated with abnormal CT scan (persistent or calcified lesion) and abnormal electroencephalogram (EEG) at the time of AED withdrawal. A practical approach may be to withdraw AED after one-year seizure-free interval in cases where resolution of lesion and a normal EEG has been documented; in other cases, AED therapy may be extended for one more year.

Corticosteroids

Steroids are required in NCC: (1) to reduce the surrounding perilesional vasogenic edema and provide symptomatic relief; (2) to prevent the presumed triggering of intense inflammatory reaction after initiation of antihelminthic treatment due to lysis and degeneration of cysts. A short course of oral prednisolone at 1–2 mg/kg/day for 5–7 days is usually used. A slightly prolonged course may be required in children with multiple NCC or when significant perilesional edema is present. In cases with acute raised ICP intravenous dexamethasone may be considered.

Definitive Therapy

Antihelminthic Therapy

The definitive therapy for parenchymal and extraparenchymal NCC differs. Until recently, the role of antihelminthic therapy for parenchymal NCC has been debated. A double-blind placebo-controlled trial in 63 children with single NCC showed significantly increased and faster disappearance of lesion within 1 month of albendazole therapy compared to placebo. Randomized controlled trials and meta-analysis of treatment studies have now shown an early resolution and less chances of seizure recurrence in children and adults treated with antihelminthic therapy when compared to no treatment. A recent meta-analysis concluded that antihelminthic therapy was associated with increased rate of seizure control and resolution of lesion in cases with single lesion. The American Academy of Neurology recommends albendazole and corticosteroids for treatment of parenchymal NCC in both children and adults. However, it is worth stressing that initiation of cysticidal therapy is not an urgency and it is preferable to wait until the child is stable before initiating antiparasitic drugs.

Albendazole/Praziquantel

Albendazole and praziquantel are the cysticidal drugs used for NCC. Albendazole is preferred over praziquantel as: (1) It has better penetration in subarachnoid space and good tolerability. (2) Concomitant use of steroids increases bioavailability of albendazole and decreases that of praziquantel. (3) Antiepileptic drugs such as phenytoin and carbamazepine decrease the bioavailability of praziquantel but do not alter that of albendazole.

In uncomplicated parenchymal neurocysticercosis, albendazole at 15 mg/kg/day in three divided doses is used for 8 days to 4 weeks. Some studies have found that a 1-week therapy with albendazole was equally efficacious as a four-week regimen for 1–3 parenchymal cysts. Multiple lesions require a four-week course. Praziquantel is used at a dose of 50 mg/kg/day in two divided doses to be taken with meals for 2 weeks.

After a single course of cysticidal therapy about 60–70% of cysts die. A repeat course of cysticidal therapy may be used in cases with

persistent lesions. Combination therapy using both praziquantel and albendazole has been found to be safe and promising. Increased levels of an intermediate sulfoxide metabolite of albendazole when a combination therapy is instituted contribute to heightened cysticidal activity.

In cases with multiple NCC with extensive edema antihelminthic therapy may initiate degeneration of all the cysts simultaneously evoking inflammation at multiple sites within the brain leading to worsening of edema. Therefore, such cases need to be treated with caution. Cysticidal therapy is contraindicated in disseminated NCC until edema is taken care of. It is also contraindicated in ocular NCC because of the risk of triggering inflammation within the eye and consequent visual loss. Once the lesions are calcified, cysticidal therapy is of no use. Cysticercal encephalitis is primarily treated with corticosteroids alongwith other symptomatic treatment for raised ICP.

Surgery

Surgical excision with endoscopic removal or open surgery with or without shunt placement is mainstay of treatment for intraventricular and subarachnoid NCC. Endoscopic cyst removal is employed for nonadherent easily accessible cysts. No consensus guideline for management of extraparenchymal cysts exists; however, most experts recommend early surgical removal of cyst whenever feasible. The most important advantage of surgical excision is immediate removal of obstruction, reduced chances of future hydrocephalus, decreased chances of shunt requirement and avoiding long-term corticosteroid therapy. In resource limited settings where neurosurgical expertise is lacking an urgent shunt placement to relieve hydrocephalus with prolonged corticosteroids and antihelminthic therapy may be used. Use of two courses of albendazole at 15 mg/kg/day for one month each, one month apart with corticosteroids has been found effective in treating intraventricular cysts with cyst resolution noted within three months of treatment.

OUTCOME

Parenchymal disease has a much better outcome compared to extraparenchymal forms and single lesion has a much better prognosis compared to multiple lesions. Single lesions usually disappear within 6 months in 60% cases. Radiological resolution must therefore be documented by repeat imaging within 3–6 months. Persisting lesions may require a repeat course of antihelminthic therapy. Seizure recurrence occurs in 10–20% cases with single NCC. Multiple NCC and calcified lesions are associated with frequent seizures and may require prolonged course of antiepileptics.

PREVENTIVE STRATEGIES

Preventive strategies aimed at blocking the transmission of tapeworm infections and eggs to humans are required to curtail the prevalence of NCC.

Transmission of Tapeworm Infections to Humans

This can be halted by prevention of human exposure to infected pork meat and by preventing infections in pigs to curb the perpetuation of infection. Human exposure can be curtailed by: (a) proper inspection of pork meat for visible cysticerci; (b) adequate cooking of pork to destroy cysticerci. Infection in pigs can be prevented by confining pigs and restricting their exposure

to human waste. Adequate large scale sanitation methods with appropriate sewage disposal systems and avoiding open defecation are vital. Community level interventions, when properly instituted have found to decrease the incidence of epilepsy in highly endemic regions. Mass community antihelminthic therapy is advocated as a measure to decrease the prevalence of NCC. The drug of choice is a single dose of niclosamide (1–1.5 g) in children or praziquantel 10 mg/kg single dose.

Vaccination of pigs with newer vaccines such as TSOL18 along with oxfendazole treatment has been found to be effective. Such programs at large scale are however not feasible in many resource constrained hyperendemic regions.

Transmission of Eggs between Humans

As transmission of eggs from asymptomatic carrier humans plays a major role in disease spread, blocking it by simple approaches such as community education regarding disease transmission, personal hygiene, hand washing and thorough washing of vegetables and fruits before cooking may be beneficial.

IN A NUTSHELL

1. Neurocysticercosis caused by *T. solium* larvae is one of the most common parasitic infections of the human brain and a common cause of acquired epilepsy in children in endemic regions.
2. Neurocysticercosis is endemic in Southeast Asia, Latin America and sub-Saharan Africa, especially in the pig-rearing or pork-eating economically deprived communities. However, it is seen worldwide.
3. Transmission of NCC is via feco-oral route usually through food handlers who are tapeworm carriers. It is perpetuated by infected pigs. Pork-eating causes taeniasis, not cysticercosis.
4. Classically, the commoner parenchymal form presents with seizures and the rarer extraparenchymal form causes raised ICP and hydrocephalus. However, the presentation can be pleomorphic.
5. Brain imaging with CT/MRI usually shows a small SEL, but multiple lesions may be seen. Identification of scolex is diagnostic of NCC.
6. Positive serologic test adds to the diagnosis of NCC; a negative test does not exclude it.
7. Cysticidal therapy is associated with increased rate of resolution of lesions and perhaps better seizure control. A short course albendazole and corticosteroids therapy is now recommended for treatment of parenchymal NCC in both children and adults.
8. Cysticidal therapy is contraindicated in disseminated and ocular NCC and has no role in calcified lesions.
9. Surgical removal of cyst with or without shunt placement is the recommended modality of therapy for intraventricular or subarachnoid NCC.
10. Neurocysticercosis is preventable—sanitation, hygiene and proper animal husbandry are essential.

MORE ON THIS TOPIC

Baranwal AK, Singhi P, Singhi S, Khandelwal N. Seizure recurrence in children with focal seizures and single small enhancing computed tomographic lesions. Prognostic Factors on Long-Term follow-Up. J Child Neurol. 2001;16:443-5.

Baranwal AK, Singhi PD, Khandelwal N, Singhi SC. Albendazole therapy in children with focal seizures and single small enhancing computerized tomographic lesions: a randomized placebo-controlled, double blind trial. Pediatric Infect Dis J. 1998;17:696-700.

Del Brutto OH. Diagnostic criteria for neurocysticercosis, revisited. Pathog Glob Health. 2012;106:299-304.

Garcia HH, Gonzalez AE, Gilman RH. Cysticercosis of the central nervous system: how should it be managed? Current Opinion in Infectious Diseases. 2011;24:423-7.

Kaur S, Singhi P, Singhi S, Khandelwal N. Combination therapy of praziquantal and albandazole versus albandazole alone in children with single lesion NCC-a randomized placebo controlled double blind trial. Ped Infect Dis J. 2009;28:403-6.

Nash TE, Garcia HH. Diagnosis and treatment of neurocysticercosis. Nat Rev Neurol. 2011;7:584-94.

Otte WM, Singla M, Sander JW, Singh G. Drug therapy for solitary cysticercus granuloma: a systematic review and meta-analysis. Neurology. 2013;80:152-62.

Singhi P, Devi Dayal, Khandelwal N. One week versus four weeks of albendazole therapy for neurocysticercosis in children: a randomized placebo controlled double blind trial. Pediatr Infect Dis J. 2003;22:268-72.

Singhi P, Dinakaran, Khandelwal NK. One year versus two years of antiepileptic therapy for SSECTL. J Trop Pediatr. 2003;5:274-8.

Singhi P, Jain V, Khandelwal N. Corticosteroids versus albendazole for treatment of single small enhancing CT lesions in children with NCC. J Child Neurol. 2004;19:323-7.

Singhi P, Ray M, Singhi S, Khandelwal N. Clinical spectrum of 500 children with neurocysticercosis and response to albendazole therapy. J Child Neurol. 2000;15:207-13.

Singhi P, Singhi S. Neurocysticercosis in children. J Child Neurol. 2004;19:482-92.

Singhi PD, Baranwal AK. Single small enhancing computed tomographic lesion in Indian children-I: evolution of current concepts. J Trop Pediatr. 2001;47:204-7.

Sinha S, Sharma BS. Intraventricular neurocysticercosis: a review of current status and management issues. Br J Neurosurg. 2012;26:305-9.

Chapter 42.19
Brain Abscess
Prashant Jauhari, Jitendra Kumar Sahu

Brain abscess is an intracranial suppurative pathology with high morbidity and mortality. It is a dynamic focal infection within the brain parenchyma, which begins as a localized area of cerebritis and evolves into a collection of pus within a well-vascularized capsule. Once formed, brain abscess can lead to permanent neurological sequelae via destruction, infarction, compression or herniation. Most commonly brain abscesses are pyogenic in nature and a significant proportion has a polymicrobial etiology. Early identification, judicious parenteral antibiotic therapy, and prompt and aggressive neurosurgical intervention are the most important components of management of such children.

EPIDEMIOLOGY

Brain abscess is the most common type of intracranial pus collection. It is prevalent worldwide. A decline in incidence has been noticed in the developed world as opposed to high incidence in economically deprived regions due to better medical facilities, better hygiene and decreased incidence of infections. Hospital-based studies from India report an average incidence of 8–15 cases/year compared with 1.5 cases/year reported from USA. Brain abscesses account for 8% of intracranial masses in developing countries and 1–2% in the developed world. Pediatric cases constitute almost 25–42% of all brain abscess patients. Congenital heart diseases have remained the most common predisposing factor. Recent epidemiological changes include a reduction in brain abscesses cases secondary to sinus and ear infections in the western world, increased detection of neonatal abscesses and increased incidence of fungal abscesses in immunocompromised children.

PATHOGENESIS/PATHOPHYSIOLOGY

Brain is a well-protected organ which is inherently resistant to infection. Entry of pathogenic microorganisms is effectively blocked by the blood-brain barrier and that is why brain abscess is a rare consequence of bacteremia, which is common in infants and children. Once the integrity of blood-brain barrier is breached seeding of the organism in a devitalized area of brain or in a region with poor microcirculation within the parenchyma becomes the foremost step in formation of brain abscess.

Route of Infection

Spread of infection or inoculation into the brain occurs by three possible routes.
1. *Contiguous spread* (25–50%) involves spread of infection from pericranial non-neural contiguous focus such as the sinuses, middle ear, dental infection or inflamed meninges as a complication of meningitis. The valveless venous channels interconnecting the intracranial and sinus mucosal veins provide an alternative intracranial access to bacteria. Dental infections may ascend to the intracranial space via aberrant venous pathways or retrograde venous flow during yawning and mastication. Dental infections, ethmoid or frontal sinusitis usually spreads to the frontal lobe, and subacute or chronic otitis media or mastoiditis preferentially spreads to cerebellum in younger children and temporal lobe in older children.
2. *Hematogenous spread* (15–30%)—From a distant focus of infection such as heart [congenital cyanotic heart disease (CCHD), bacterial endocarditis], lungs (empyema), skin and intra-abdomen. Abscess site follows a distribution that reflects the cerebral arterial supply, most commonly that of the middle cerebral artery. Hematogenous spread can also occur by way of the veins that drain into the cavernous sinus, resulting in frontal lobe abscesses that are often correlated with infections of the facial tissues or ethmoidal sinuses.
3. *Direct inoculation* (8–15%)—Secondary to compound skull fractures, scalp wounds anterior cranial fossa or temporal bone fractures, chronic cerebrospinal fluid (CSF) fistula and neurosurgical procedures.

Brain abscess resulting from contagious spread is usually single, while multiple brain abscesses mostly result from hematogenous spread.

Stages of Abscess Formation

The natural evolution of brain abscess can be divided into four distinct stages **(Table 1)**. The abscess begins as a focal area of infection with surrounding edema and inflammation. Within a few days, central necrosis starts to occur which progresses outward and ultimately liquefies the affected area. Within weeks, this area gets walled off by a collagenous capsule formed by the accumulating fibroblasts limiting the spread. Within 3–4 weeks, a dense fibrous capsule is formed which is amenable for resection. Further with increasing pressure within the capsule microorganisms escape out and form daughter abscesses in the adjoining area **(Fig. 1)**. Animal studies have demonstrated that abscesses mostly occurred in the white matter or at the gray-white matter junction and gradually migrate to the ventricle. The abundant capillary beds at these sites facilitate frequent lodging of the bacteria and development of brain abscess. The capsule of the abscess is thickest toward the meninges and thinnest toward the ventricle and, therefore, increased chances of rupture within the ventricular system. Pediatric brain abscesses are supratentorial in 85%, infratentorial in 13% and combined location in 2% cases.

Predisposing Factors

The most common predisposing factors for brain abscess in childhood are cyanotic congenital heart diseases, sinus and otogenic infections and dental infections and procedures. Other

Table 1 Histological stages of brain abscess

Stages	Duration	Histological features
Stage I: Early cerebritis	1–3 days	Microglia and astrocyte activation, neutrophil accumulation, edema and tissue necrosis
Stage II: Late cerebritis	4–9 days	Macrophage and lymphocyte infiltration. Expansion of the cerebritis and formation of central necrotic focus
Stage III: Early capsulation	10–14 days	Formation of a ring enhancing dense collagenous and vascularized abscess capsule with peripheral gliosis and fibrosis
Stage IV: Late capsulation	Beyond 14 days	Thickening of abscess capsule. Focal suppuration completely walled off. Abscess amenable to excision within 3–4 weeks.
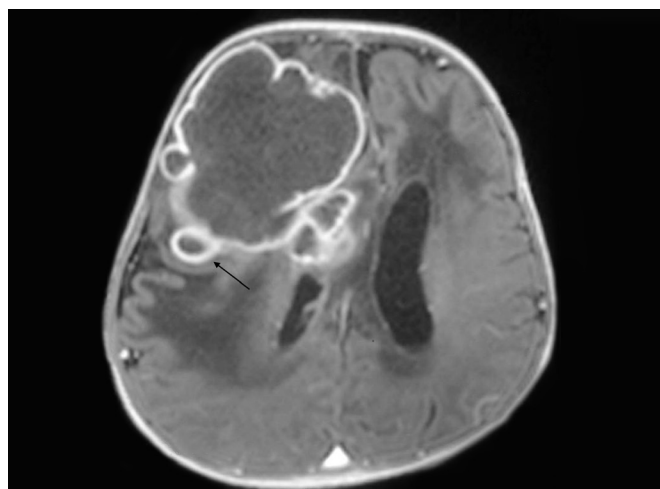
Figure 1 Axial T1-weighted MRI section with gadolinium in a 4-month-old infant shows presence of a large intracerebral abscess with budding daughter cysts. Associated vasogenic edema and midline shift could also be seen

Figure 2 CECT head of a 1-year-old girl with cyanotic congenital heart disease shows multiple pyogenic brain abscesses

risk factors identified are immunosuppression, neurosurgical procedures such as ventriculoperitoneal shunts, penetrating skull injury and comminuted fracture of the skull, and congenital lesions of the head and neck (dermal sinuses). Infreqently, brain abscess occurs as a complication of pyogenic meningitis. Occasional reports of brain abscess following aspiration of foreign bodies, esophageal endoscopy and ocular trauma exist in literature. In a significant proportion of children (14–25%), no identifiable predisposing factor is found (cryptogenic brain abscess).

Unoperated CCHD accounts for 25–46% of brain abscess cases in children. The incidence of brain abscess in children with CCHD is approximately 2%. Intracardiac right-to-left shunt bypasses the pulmonary circulation and therefore allows bacteria to gain direct entry into the cerebral circulation. In addition, polycythemia secondary to decreased arterial oxygenation and hyperviscosity cause a focal area of ischemia and necrosis that acts as a nidus for infection forming a cerebral abscess. However, this complication of CCHD rarely develops before 2 years of age, after which, the risk of abscess formation increases consistently till 12 years of age with a peak incidence between 4 and 7 years of age. The most common form of cyanotic congenital heart disease associated with brain abscess is tetralogy of Fallot (45%) **(Fig. 2)**. Other common CCHD associated with brain abscess are complete transposition of the great arteries and double outlet of right ventricle. An associated endocarditis is rare in these cases, although acute bacterial endocarditis in itself is an independent predisposing factor for brain abscess. A reverse blood flow across patent foramen ovale during valsalva may allow paradoxical septic emboli to reach the cerebral vasculature.

Otorhinogenic sepsis is another important risk factor for brain abscess in children and adolescents. In India, chronic suppurative otitis media constitutes up to 50% cases of brain abscess across all ages. Immunosuppression is recognized as a major predisposing factor for brain abscess. Infections with HIV, malignancy, iatrogenic immunosuppression with long-term steroid therapy, chemotherapeutic agents, and organ transplant patients have increased susceptibility for intracranial suppuration secondary to atypical or opportunistic organisms.

Brain abscess as a complication of meningitis is rare with meningitis constituting approximately 12–36% of overall brain abscess cases in childhood particularly in infants and toddlers. Meningitis may occur concomitantly during the incipient stages of abscess formation after an organism has seeded the brain parenchyma from a contiguous extracranial source. In such scenarios, meningitis is a consequence of brain abscess instead of the opposite being true. Neonates with meningitis due to atypical pathogens such as *Citrobacter* and *Enterobacter Sakazakii* have increased chances of developing brain abscess.
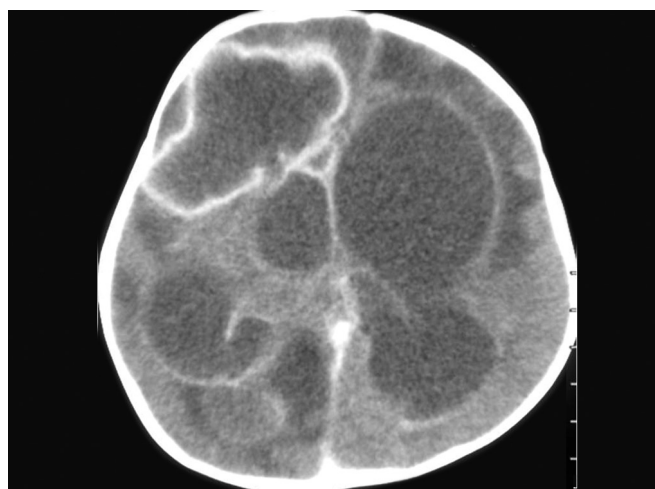
ETIOLOGY

In immunocompetent children, majority of abscess are bacterial in origin (50–60%). The most common microorganisms causing brain abscess in children worldwide are aerobic and anaerobic streptococci. **Table 2** mentions the other common pathogens identified in pediatric brain abscess. Polymicrobial etiology is seen in a third of cases. In at least 15–30% of childhood brain abscess, no etiological agent could be identified. **Table 3** provides the most common microorganism associated with brain abscess based on the predisposing source of infection. In immunocompromised children, atypical pathogens such as fungal organisms and mycobacterium are commonly seen.

CLINICAL FEATURES

The signs and symptoms of brain abscess are nonspecific at the onset. The classical triad of headache, fever and focal neurological signs is rare. Broadly, the clinical features results from any of the four clinical syndromes namely focal mass expansion, intracranial hypertension, diffuse destruction and focal neurological deficits.

Table 2 Usual pathogens associated with pediatric brain abscess

Microorganism	Percentage
Streptococcal species	60–70
Gram-negative anaerobic bacilli	20–40
Enterobacteriaceae	20–30
S. aureus	10–15
Fungi	1–5
Mycobacterium	4

Table 3 Source of infection, probable etiological agent and site of abscess

Source of infection	Probable pathogens	Site of brain abscess
Paranasal sinus	Viridans and anaerobic streptococci, *Haemophilus* sp., *Fusobacterium* sp., *Bacteroides* sp. (nonfragilis)	Frontal lobe
Otogenic	Gram-negative enteric bacilli, *Bacteroides* sp. (including *B. fragilis*), streptococci, *P. aeruginosa*	Temporal lobe cerebellum
Odontogenic	Steptococci, Gram-negative bacilli, *B. fragilis*	Frontal lobe
CCHD	Streptococci	Parietal/multiple
Endocarditis	*Viridans* streptococci, *S. aureus*	Parietal/multiple
Surgical procedures	*S. epidermidis, S. aureus, P. aeruginosa*	At operative site
Penetrating trauma	*S. aureus*, aerobic streptococci	At trauma site
Immunosuppression	*Nocardia*, fungi, *Mycobacterium*	Variable

Abbreviation: CCHD, congenital cyanotic heart disease

The symptom constellation depends upon several factors such as predisposing risk factor, age, size, site and number of abscess. A nonspecific headache is the most common symptom in older children and adolescent. In infants, irritability, excessive crying on handling and fussiness is the initial complaint followed by lethargy, fever, vomiting, bulging fontanel, frequent seizures and increase in head circumference.

Intracranial abscess is an exception to the general belief that pus collection is associated with high-grade fever. Fever may be present only in 50–80% and, therefore, its absence should not exclude the diagnosis. Similarly, focal deficits are seen in not more than half of the cases. The frequencies of various clinical symptoms are provided in **Table 4**.

As the abscess evolves, surrounding vasogenic edema increases and results in midline shift and worsening signs of raised intracranial pressure (ICP) and impending herniation. Sudden worsening of sensorium, high-grade fever, severe headache and meningismus may suggest rupture of abscess into the ventricular cavity. Depending upon the involved cerebral lobe specific dysfunction in brain function is observed **(Table 5)**. Frontal and parietal lobes are the two most common sites respectively. Brainstem abscess are very rare (< 2%). Pontine abscesses may compress aqueduct of Sylvius and cause obstructive hydrocephalus. Typical brainstem syndromes are generally not seen due to longitudinal rather than lateral spread of the abscess.

DIAGNOSIS

Mainstay of diagnosis is visualization of the abscess on imaging. Most of the laboratory investigations remain unremarkable.

Neuroimaging

Magnetic Resonance Imaging of Brain

Magnetic resonance imaging (MRI) of brain with gadolinium is the imaging modality of choice for diagnosing brain abscess. It is superior to computed tomography (CT) scan in identifying early stages of cerebritis, microabscesses, brainstem and cerebellar pus collections. MRI can also aid in identifying nearby sources of infection such as sinusitis or mastoiditis. On T1-weighted images, brain abscess appears as a hypointense lesion with ring enhancement on gadolinium administration. On T2-weighted images, it appears as a central hyperintense lesion encircled by a uniform hypointense capsule and surrounded by an irregular hyperintense area of perilesional edema.

Newer modalities of MRI imaging such as diffusion-weighted imaging (DWI) can further differentiate between brain abscess

Table 4 Clinical features of brain abscess

Clinical symptom	Percentage	Clinical symptom	Percentage
Headache	50–80%	Meningismus	25–50%
Fever	60–80%	Alteration of sensorium	30–50%
Vomiting	20–70%	Unconsciousness	10–20%
Focal deficits	35–50%	Hydrocephalus	6–17%
Seizures	20–25%	Papilledema	30–40%

Table 5 Clinical symptomatology of brain abscess based on specific cerebral region involved

Cerebral region	Clinical characteristics
Frontal lobe	Sinus/dental infection common; initially silent, drowsiness, personality change, seizures, appearance of primitive reflexes, hemiparesis
Parietal lobe	Hematogenous spread common; visual field defects inferior quadrantanopia to homonymous hemianopia Dominant hemisphere: Dysphasias; nondominant hemisphere: dyspraxia and spatial neglect
Temporal lobe	Associated otogenic infection common; dominant hemisphere: dysphasias; nondominant hemisphere: superior quadranopsia
Occipital lobe	Homonymous hemianopia; rupture into ventricle causing ventriculitis/ependymitis; septic thrombophlebitis of the transverse sinus
Cerebellum	Uncommon; appendicular and gait ataxias; eye movement abnormalities
Brainstem	Multiple cranial nerve palsies; obstructive hydrocephalus

and necrotic tumors. Proton MR spectroscopy is useful in differentiating between abscess, radiation necrosis other cystic lesions. Perfusion MRI with dynamic intravenous contrast injection studies can differentiate between these lesions by analyzing the vascularity of the lesion and blood flow. Thallium single-photon emission computed tomography and fluorine-18 fluorodeoxyglucose positron emission tomography have been effective in adults in differentiating brain abscess from tumor in doubtful cases. However, its role in pediatric cases has not been extensively studied. Radiological appearance of brain abscess on various MR sequences is tabulated in **Table 6**.

Computed Tomography of Head

Computed tomography is helpful in identifying the site, number and location of brain abscess in most cases and can be used for monitoring the progression of disease after initiation of antimicrobial therapy or surgical drainage. It can also detect other abnormalities such as subdural empyema, leptomeningeal enhancement, ventriculitis and hydrocephalus. The appearance of lesion depends upon the evolutionary stage of abscess. Initially during early cerebritis, it may appear as a low signal area with mass effect and may not show enhancement with contrast. In later phases, the typical finding is of a hypodense lesion with thin uniform ring enhancement on contrast-enhanced CT (CECT) imaging.

High-resolution cranial ultrasonography can be used in neonates and infants with open anterior fontanel for diagnosis of brain abscess and subdural empyema.

Cerebrospinal Fluid Analysis

Brain abscess is an exceptional central nervous system infection where lumbar puncture (LP) is contraindicated. Often, due to mass effect and vasogenic edema, the ICP is asymmetrically raised and LP may cause sudden herniation and collapse. Also in cases where LP is performed, it failed to aid in the diagnosis of brain abscess. One has to remember that unless brain abscess has ruptured into the ventricular system or concomitant meningitis exists, CSF analysis may be unremarkable. Most common CSF findings in brain abscess are mild mononuclear pleocytosis, mildly elevated protein and normal to slightly low sugars with sterile cultures. CSF culture is positive in less than 10% cases only. Once ventriculitis sets in secondary to rupture of abscess into the ventricles, CSF may show marked leukocytosis with 50,000–100,000 cells, significant

Table 6 Radiological appearance of brain abscess on MRI

MRI sequences	Appearance
T1 weighted	Central low intensity Peripheral low intensity (perilesional edema)
T1 weighted with gadolinium	Ring enhancement
T2 weighted/FLAIR	Central high intensity Peripheral high intensity (perilesional edema) Capsule appear as thin rim of intermediate to slightly low signal intensity
DWI	High DWI signal centrally Low signal on ADC
Perfusion MRI	Reduced relative cerebral blood volume
MRS	Elevated succinate and lactate peaks Choline: creatine and NAA peaks reduced

Abbreviations: FLAIR, fluid attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; NAA, n-acetyl aspartate; MRS, magnetic resonance spectroscopy

hypoglycorrhachia (CSF sugar < 40 mg/dL), raised proteins and elevated lactate (> 500 mg%).

Other Investigations

Nonspecific biochemical signs of infection such as moderate leukocytosis, elevated C-reactive protein and erythrocyte sedimentation rate are present. Blood cultures are often sterile unless hematogenous spread of infection has occurred. Definite diagnosis of brain abscess is made only with histopathological examination of brain tissue, demonstration of pus and identification of etiological agent. Specimen obtained from stereotactic aspiration or excision biopsy must be subjected to Gram stain, aerobic, anaerobic, acid-fast bacilli and fungal cultures. As brain abscesses are frequently polymicrobial, newer modalities such as 16S ribosomal DNA polymerase chain reaction amplification may be utilized to increase the number of identifiable bacterial species as opposed to standard cultures.

Search for Source of Infection

A thorough and extensive search for the source of primary infection should be done in all cases. Identification of an infective site may provide a clue to the etiological agent and guide in antimicrobial therapy. Sinus and otogenic infections can be simultaneously identified on MRI brain. Ear and oral cavity inspection is indispensible in all cases of brain abscess as is the screening of heart through echocardiography. Consecutive blood cultures may be required if endocarditis is suspected.

DIFFERENTIAL DIAGNOSIS

Brain abscess needs to be differentiated from other causes of intracranial suppuration and space occupying lesions as well as with more diffuse forms of CNS infection such as viral encephalitis. Herpes encephalitis with frequent focal neurological signs may mimic a brain abscess. Subdural empyema, another form of intracranial suppuration often presents with high-grade fever and prominent meningismus which is usually not seen with brain abscess. Tuberculoma and neurocysticercosis commonly present as first episode of afebrile seizure and generally are not associated with progressive neurological signs. Primary brain tumors have a more indolent course and slow progression over months unless complicated by bleed, secondary infection or obstructive hydrocephalus. It may not be always possible to differentiate these on clinical ground and neuroimaging is required for diagnostic clarification. It is prudent to say that even early CT findings are nonspecific for brain abscess. Early edema with mild-to-moderate mass effect on CT may be seen with tumor, stroke and parasitic infections. Stroke resulting from vasculitis may mimic MRI findings of cerebritis. Newer MRI modalities such as DWI, proton magnetic resonance spectroscopy (MRS) and perfusion scans are required in doubtful cases.

MANAGEMENT

Successful treatment of brain abscess requires prompt and appropriate antimicrobial therapy combined with surgical drainage in most cases. If surgical excision or drainage is planned, it should be performed early in the course of therapy.

Antimicrobial Therapy

Choice of Antibiotics

Treatment with antibiotics is commenced as soon as the diagnosis is established on imaging on an empirical basis. The initial choice is a combination of broad-spectrum antibiotics with good CNS penetration. The empirical antibiotic regime must provide

cover for anaerobes (third-generation cephalosporins and metronidazole) and include vancomycin if methicillin-resistant *Staphylococcus aureus* is suspected or history of penetrating trauma or neurosurgical intervention is present. Further antibiotic therapy would depend upon the culture and antibiotic sensitivity. If cultures fail to show any organisms, these antibiotics should be continued. Suggested choice of antibiotics according to site of infection and probable organism is provided in **Box 1**.

Duration of Antibiotics
The exact duration of antibiotics required for treatment of brain abscess is unclear. Most authors recommend a 4–6 weeks intravenous antibiotic therapy for surgically drained bacterial abscess and a 6–8 weeks therapy when medical therapy is solely offered. Immunocompromised children may require a longer duration with additional cover for atypical organisms. Cerebritis may require a shorter duration compared to a fully encapsulated abscess. Multiloculated abscess or abscesses may require a longer therapy.

Role of Oral Antibiotics
No data is available to recommend or refute oral antibiotic therapy. However, oral drugs often fail to penetrate blood-brain barrier and do not achieve the minimal inhibitory concentration for most of the microorganisms within the abscess. This method of completing antibiotic course must be reserved for those cases where drug sensitivity of the isolated organisms shows good sensitivity to any of the oral medications known to have good CNS penetration.

Surgical Treatment
Neurosurgeon should be involved early in the course of therapy. Indications for Surgical management are provided in **Box 2**. The surgical management may be in form of excision or drainage. Drainage is either performed through burr hole, craniotomy or stereotactically. The choice of surgical procedure has not been found critical in deciding the outcome of the case and should depend upon the surgical expertise available and the hemodynamic status of the child. Deep-seated abscess, small abscess and those involving eloquent cortical regions are preferably drained using stereotactic aspiration and aspiration via craniotomy or craniectomy or excision is performed in superficial abscess or abscess located in the posterior fossa.

Supportive Care
Raised intracranial pressure is often seen and treatment must be directed to symptomatic management of raised ICP. Headache and fever may show complete or partial response to regular

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BOX 1 Suggested empirical antibiotic therapy for brain abscess
If predisposing factor is of oral, sinus or otogenic origin: Ceftriaxone (100 mg/kg/day in two divided doses)/cefotaxime (200 mg/kg/day in two divided doses)* *plus* metronidazole (15 mg/kg IV loading followed by 7.5 mg/kg IV eight hourly)
If cyanotic congenital heart disease is the predisposing factor: Ampicillin-sulbactam (50–100 mg/kg 6 hourly) alone *or* ceftriazone/cefotaxime (dosage as above) *plus* metronidazole (dosage as above)
In postoperative brain abscess: *Ceftazidime (50 mg/kg/dose 8 hourly) *or* cefepime (50 mg/kg/dose 8–12 hourly *or* meropenem (40 mg/kg/dose 8 hourly) *plus* vancomycin (60 mg/kg/day in 3–4 divided doses)**
*Ceftazidime (50 mg/kg/day q 8 hourly) may be considered if *Pseudomonas* suspected.   **Replace with cloxacillin/oxacillin/nafcillin if culture reveals methicillin-sensitive *Staphylococcus aureus*.

BOX 2 Indications for surgical drainage of brain abscess
• Abscess larger than 2.5 cm   • Aspiration of larger abscesses involving noneloquent cortex in cases of multiple abscesses.   • When abscess size is increasing after 2 weeks of antibiotic therapy   • No decrease in abscess size after 3–4 weeks of antibiotics   • Multiloculated abscess   • Traumatic abscesses with bone chips or foreign material   • Fungal brain abscesses

antipyretics. The role of corticosteroids in treatment of brain abscess is controversial. Studies have shown that steroid inhibit capsule formation, interfere with inflammatory response, decrease antibiotic concentration inside the abscess, increases risk of ventricular rupture and alter CT findings. They are however indicated in children with signs of impending herniation secondary to mass effect caused by massive perilesional edema.

Antiepileptics are required in all children who develop seizures. Phenytoin, carbamazepine, and valproate are equally effective. The duration of antiepileptics depends upon the imaging and electroencephalographic findings. Generally, a 1–3 months course is sufficient, provided no further seizures have occurred.

Monitoring and Follow-up
Magnetic resonance imaging of brain or CT scan can be used for monitoring response to therapy. A repeat CECT should be done urgently in case of sudden neurological deterioration. Else, it is to be repeated after 2–4 weeks of initiation of medical therapy to document the change in size of abscess and resolution.

Management of Brain Abscess in an Immunocompromised Child
Apart from the typical bacterial organisms, *Mycobacterium tuberculosis* and fungal organisms such as *Aspergillus, Nocardia, Candida* and *Mucor* are the common causes of brain abscess. Empirical therapy should be avoided in immunocompromised patients and every effort should be made in establishing a microbiological diagnosis.

PROGNOSIS AND OUTCOME
Brain abscess in children is associated with very high mortality and morbidity. With advent of newer neuroimaging modalities, antibiotic therapy, the mortality has reduced from 30–60% in the preimaging era to 3–25%. Mortality is directly related to the neurological status at admission. Rupture of abscess into the ventricles and posterior fossa location are associated with rapid deterioration and a very high mortality rate. Poor prognostic markers noted by various authors are provided in **Box 3**. Common neurological sequelae are delayed onset seizures (commonly seen with frontal lobe abscess), mental retardation and focal neurological deficits.

BOX 3 Poor prognostic markers of brain abscess
• Neonatal or infantile age group   • Rapidly progressive symptomatology before hospitalization   • Low Glasgow Coma Score at admission   • Rupture into ventricles   • Posterior fossa location   • Multiloculated multiple abscesses   • Immunocompromised state   • Fungal abscess

IN A NUTSHELL

1. Brain abscess is a focal intraparenchymal pus collection with microorganism seeding occurring from contiguous, hematogenous or direct inoculation.
2. Untreated CCHD and sino-otic infections are the most common predisposing risk factors for pediatric brain abscess.
3. Brain abscess associated with hematogenous spread are often multiple in number and generally located in the distribution of middle cerebral artery.
4. The most common microorganisms causing brain abscess in children worldwide are aerobic and anaerobic streptococci.
5. The causative organism usually depends upon immune status of the child and source of primary infection. In 30% cases, brain abscess is polymicrobial.
6. Magnetic resonance imaging of brain with gadolinium is the imaging modality of choice for diagnosing brain abscess.
7. Lumbar puncture is contraindicated in brain abscess with significant mass effect due to risk of sudden herniation and collapse.
8. Successful treatment of brain abscess requires prompt and appropriate antimicrobial therapy combined with surgical drainage in most cases.
9. Broad-spectrum antibiotic cover until culture reports are available should be empirically initiated. Duration of antibiotic treatment should be at least 4–6 weeks in surgically drained abscess and 6–8 weeks in surgically untreated cases.
10. Follow-up CECT should be done urgently in case of sudden neurological deterioration or after 2–4 weeks of initiation of medical therapy.

MORE ON THIS TOPIC

Arlotti M, Grossi P, Pea F, et al. Consensus document on controversial issues for the treatment of infections of the central nervous system: Bacterial brain abscesses. Int J Infect Dis. 2010;14:S79-92.

Atiq M, Ahmed US, Allana SS, et al. Brain abscess in children. Indian J Pediatr. 2006;73:401-4.

Felsenstein S, Williams B, Shingadia D, et al. Clinical and microbiologic features guiding treatment recommendations for brain abscesses in children. Pediatr Infect Dis J. 2013;32:129-35.

Frazier JL, Ahn ES, Jallo GI. Management of brain abscesses in children. Neurosurg Focus. 2008;24:E8.

Infection in Neurosurgery Working Party. The rational use of antibiotics in the treatment of brain abscess. Br J Neurosurg. 2000;14:525-30.

Lakshmi V, Umabala P, Anuradha K, et al. Microbiological spectrum of brain abscess at a tertiary care hospital in South India: 24-year data and review. Patholog Res Int. 2011;58:31-9.

Manzar N, Manzar B, Kumar R, Bari ME. The study of etiologic and demographic characteristics of intracranial brain abscess: a consecutive case series study from Pakistan. World Neurosurg. 2011;76:195-200.

Moorthy RK, Rajshekhar V. Management of brain abscess: An overview. Neurosurg Focus. 2008;24:E3.

Nathoo N, Nadvi SS, Narotam PK, Van Dellen JR. Brain abscess: management and outcome analysis of a computed tomography era experience with 973 patients. World Neurosurg. 2011;75:716-26.

Ozsürekci Y, Kara A, Cengiz AB, et al. Brain abscess in childhood: a 28-year experience. Turk J Pediatr. 2012;54:144-9.

Sáez-Llorens X. Brain abscess in children. Semin Pediatr Infect Dis. 2003;14:108-14.

Shachor-Meyouhas Y, Bar-Joseph G, Guilburd JN, et al. Brain abscess in children: epidemiology, predisposing factors and management in the modern medicine era. Acta Paediatr. 2010;99:1163-7.

Chapter 42.20
Inflammatory Demyelinating Disorders
Bindu PS

The inflammatory demyelinating disorders of the central nervous system comprise a spectrum of disorders affecting the white matter of the brain and the spinal cord. Demyelination or loss of myelin of the white matter which is a key feature of these disorders can be either primary or secondary. The secondary demyelinating disorders result from infectious, ischemic, metabolic or hereditary disorder. The etiology of primary demyelinating disorders is unclear but thought to be multifactorial. The primary demyelinating disorders constitute a heterogenous group of disorders and include acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome, pediatric multiple sclerosis (MS) and neuromyelitis optica (NMO). These conditions can be monophasic, relapsing remitting or progressive and can have a highly localized or diffuse involvement of the central nervous system. The prognostic and therapeutic implications necessitate a proper diagnostic classification of these disorders at onset.

The International Pediatric Multiple Sclerosis Study Group has proposed consensus definitions for demyelinating disorders in children to aid in standardization of diagnosis, investigations and further research. This chapter discusses the consensus definitions, different clinical phenotypes, differential diagnoses, diagnostic evaluation and approach to classification, management and outcome of primary inflammatory demyelinating disorders of the central nervous system in children.

DEFINITIONS

The International Pediatric Multiple Sclerosis Association has formulated consensus definitions for diagnosis of acute demyelinating disorders in children **(Table 1)**.

EPIDEMIOLOGY

The demographic characteristics and geographic distribution vary widely among different groups of demyelinating disorders. The incidence of acquired demyelinating diseases in population-based studies range between 0.66 and 1.66 per 100,000 population.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Epidemiology
Mean age at presentation of pediatric ADEM ranges between five and eight years. Gender ratio is either balanced or shows male preponderance. Data on the incidence of ADEM are sparse. Prevalence is expected to be high in resource poor settings because of the proposed role of antecedent infections in the etiology of acute demyelinating disorders.

Etiopathogenesis
Etiology of ADEM is not clear. A high incidence of seasonal distribution and diverse antecedent viral and bacterial diseases reported in patients with ADEM links to an infectious etiology. The pathogenesis is autoimmune-mediated and is based on *molecular mimicry*. The infectious agents serve as an antigenic trigger which

shares epitopes with various autoantigens of myelin such as myelin basic protein and myelin oligodendrocyte protein. The antigenic trigger activates the T-cells which cross the blood-brain barrier and react against myelin epitopes. Vaccines especially the influenza, rabies and smallpox vaccines have been reported to precipitate ADEM. Pathologically, ADEM is characterized by periventricular infiltrates of lymphocytes, macrophages and occasional plasma cells with edematous and demyelinated adjacent white matter. Multifocal and diffuse lesions are found in gray matter, white matter and spinal cord. All lesions are of the same age and axonal injury is minimal.

Clinical Features
The presentation of ADEM can be wide and range from minimal symptoms to a fulminant course. Children may present with multifocal neurological signs such as hemiparesis, paraparesis, unilateral or bilateral pyramidal signs, cranial nerve deficits, ataxia, visual loss due to optic neuritis, seizures, slow or slurred speech or aphasia and sensory symptoms. Respiratory failure secondary to brainstem involvement or severely impaired consciousness can occur. A rapidly progressive course with resultant mortality is seen in fulminant form of ADEM. Multiphasic ADEM refers to two episodes consistent with ADEM separated by three months but not followed by any further events. Recurrent ADEM is a rarity and has been eliminated from the recent classifications. Relapsing diseases which follows after the second episodes of ADEM indicates a chronic disorder, most often leading to the diagnosis of MS or NMO.

Diagnostic Evaluation
Magnetic resonance imaging shows multiple lesions which are large 1–2 cm diameter **(Figs 1A to F)**. Gadolinium enhancement in one or more lesions can be seen. Different patterns of contrast enhancement can be present and include open ring and nodular enhancement. Periventricular lesions are less common relative to MS, but lesion number location and size are variable. Hypointense lesions on magnetic resonance imaging are rare in ADEM. Lesions in the thalamus and basal ganglia are more typical of ADEM than in MS. Extensive lesions in spinal cord also suggest the diagnosis of ADEM.

Spinal fluid examination is mandatory in a child who presents with acute neurological deficit. Cerebrospinal fluid findings are usually abnormal showing a moderate pleocytosis with elevated protein content. The presence of cerebrospinal fluid pleocytosis does not differentiate ADEM from clinically isolated syndrome or NMO. Cerebrospinal fluid oligoclonal bands may be seen in ADEM but tend to be transient.

Treatment
Treatment of acute inflammatory demyelinating disease requires that other possible diagnoses, especially infectious, neoplastic and metabolic disorders are carefully excluded. The mainstay of acute therapy for all inflammatory demyelinating central nervous system disorders are corticosteroids. Intravenous steroids are required to shorten the acute inflammatory process and hasten recovery. Subsequent oral steroid taper for a duration of 4–6 weeks is recommended for ADEM. Duration of taper less than 3 weeks has been associated with an increased risk of relapse.

Prognosis
Acute disseminated encephalomyelitis is a monophasic illness. The risk factors for MS following a first episode of acute demyelination

Table 1 Definitions of acquired demyelinating disorders

Disorder	Definitions
Acquired demyelinating encephalomyelitis	1. A first polyfocal clinical CNS event with presumed inflammatory cause. 2. Encephalopathy that cannot be explained by fever is present. 3. No new clinical and MRI findings emerge three months or more after the onset 4. Brain MRI abnormal during the acute phase 5. *Typically on MRI:* Diffuse poorly demarcated large (> 1–2 cm) lesions involving predominantly the cerebral white matter; T1 hypointense lesions are rare; deep gray matter lesions (e.g., thalamus and basal ganglia) can be present
Recurrent ADEM	This was defined previously as a new event of ADEM with a recurrence of the initial symptoms and signs, 3 or more months after the first ADEM event, without involvement of new clinical areas by history, examination, or neuroimaging. *Now this has been subsumed under multiphasic ADEM.*
Multiphasic demyelinating encephalomyelitis	ADEM followed by a new clinical event also meeting criteria for ADEM, but involving new anatomic areas of the CNS as confirmed by history, neurologic examination, and neuroimaging. The event must develop within 3 months of the initial event.
Pediatric multiple sclerosis	1. Two or more nonencephalopathic CNS clinical event separated by more than 30 days, involving more than one area of CNS. 2. Single clinical event and MRI features consistent with 2010 revised McDonald criteria* for dissemination in space and time. 3. ADEM followed three months later by a nonencephalopathic clinical event with new lesions on MRI consistent with MS

Neuromyelitis optica (NMO)	1. Optic neuritis
	2. Acute myelitis as major criteria and
	3. At least two of the three supportive criteria
	    a. Contiguous spinal cord MRI lesion extending over three or more segments
	    b. Antiaquaporin-4-IgG seropositive status
	    c. Brain MRI not meeting the diagnostic criteria for MS

Clinically isolated syndrome (CIS)	1. A first acute clinical episode of CNS symptoms (without encephalopathy) with a presumed inflammatory demyelinating cause 2. Absence of prior clinical history of CNS demyelinating disease. 3. No encephalopathy (no alteration in consciousness or behavior that cannot be explained by fever) 4. The diagnosis of MS based on baseline magnetic resonance features is not met.

Adapted from Krupp et al. 2007 and 2013

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis.

*The 2010 Revised McDonald criteria for dissemination in space require one or more T2 lesion in at least two out of the four locations: periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald criteria for dissemination in time can be satisfied by the emergence of new T2 lesions (with or without enhancement) on serial scans or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

include age greater than 10 years, absence of encephalopathy, absence of precipitating infection, presence of optic neuritis, presence of intrathecal oligoclonal bands, family history of MS and periventricular perpendicular ovoid lesions (PPOL). Factors associated with a decreased relapse include age less than 10 years of age, encephalopathy, postinfectious presentation, isolated transverse myelitis, meningism or seizures. Comparison of clinical and magnetic imaging features between acute disseminated encephalomyelitis and multiple sclerosis is given in **Table 2**.

PEDIATRIC MULTIPLE SCLEROSIS

Epidemiology

About 3–10% of the MS patients manifest during childhood. Gender ratio varies with age. A female preponderance is reported in patients with onset of MS in adolescence. However, there is no gender predilection in children presenting with MS before 6 years of age.

Etiopathogenesis

Environmental factors have been implicated in the susceptibility of children to multiple sclerosis. Three important factors are: (1) vitamin D deficiency; (2) viral infections, particularly Epstein-Barr virus, herpes virus and varicella zoster; (3) exposure to cigarette smoke. Parental smoking has been identified as a risk factor with an

increased level of risk after longer duration of exposure. Currently, there is no evidence on possible triggering events of vaccination on the manifestation of pediatric MS. Studies have shown that in children vaccinated after the first episode of demyelination neither tetanus nor hepatitis B vaccination increased the risk of conversion.

Clinical Features

Diagnosis of multiple sclerosis is defined by recurrent attacks of inflammatory demyelination. Presenting features include motor deficits, sensory dysfunction, brainstem symptoms, optic neuritis and ataxia. Isolated transverse myelitis is an uncommon presentation of MS in children. Optic neuritis in MS tends to be unilateral compared to NMO. The diagnosis of pediatric MS requires multiple episodes of central nervous system demyelination separated in time and disseminated in space. In patients less than 10 years of age, the dissemination in time and space should be preferably a clinical one and secondly the diagnosis of ADEM should be excluded. The prognosis in the patients less than ten years of age is generally good. Most patients in the adolescent age group experience the second attack of demyelination within 1 year, whereas children below 10 years have a longer attack interval. Even though the course is most often relapsing remitting in the beginning, patients develop permanent physical disability, spasticity, tremor, or bladder dysfunction over time.
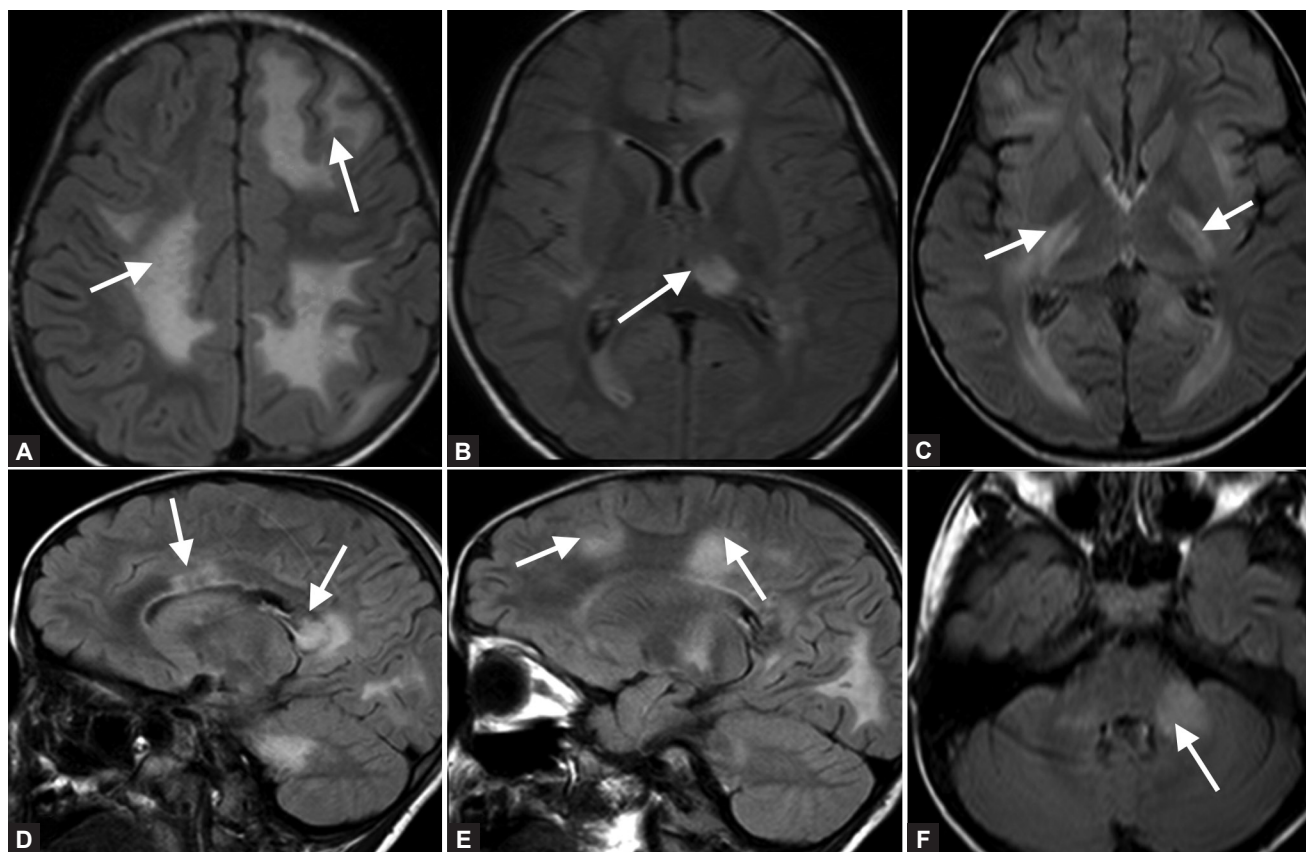
Figures 1A to F Brain magnetic resonance imaging in a 7-year-old boy with acute disseminated encephalomyelitis. White matter lesions are present in A (axial view) and E (sagittal view): Lobar white matter; (B) Thalamus; (C) Internal capsule; (D) Corpus callosum; (F) Middle cerebellar peduncle

Table 2 Comparison of clinical and magnetic resonance imaging features between acute disseminated encephalomyelitis (ADEM) and multiple sclerosis

Characteristics	ADEM	Multiple sclerosis
Age of onset	Younger	Older
Gender preference	Nil	Female preponderance
Antecedent event	Common	Uncommon
Prodormal symptoms	Common	Uncommon
Onset	Acute	Subacute
Headache, vomiting, fever	More common	Less common
Altered sensorium	More common	Unlikely
Seizures	More common	Less common
Meningism	More common	Less common
Pattern of CNS involvement	Usually multifocal	Usually single site
Optic neuritis	Bilateral	Unilateral
Transverse myelitis	Complete	Incomplete
CSF protein	Elevated	Normal/mild elevation
CSF pleocytosis	Variable	< 50/cmm
CSF oligoclonal bands/intrathecal IgG production	Transient	Persistent
MRI lesion load	Extensive (Symmetric/asymmetric)	Scattered asymmetric
MRI—white matter distribution	Usually subcortical	Usually periventricular
MRI—corpus callosum involvement	Less common	Common
MRI—predominant brainstem involvement	More common	Less common
MRI—thalamus, basal ganglia involvement	More common	Less common
MRI—lesion margin	Ill-defined	Defined
MRI—enhancement of lesions with contrast	Usually uniform	Nonuniform
Serial MRI	Resolution of lesions; no fresh lesions, new lesions occur only in association with symptoms	Asymptomatic lesions can be seen

The Kurtze *expanded disability status scale* (EDSS) is a method of quantifying disability in multiple sclerosis. The scale quantifies disability in five functional systems namely pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and others. This allows the physician to assign a score in each of these systems. Retrospective longitudinal studies of pediatric onset MS patients indicate that majority of the patients will progress to secondary progressive MS. Primary progressive MS in which patients experience progressive disability from onset without clinical relapses is exceptionally rare in children. There are no serologic or immunologic factors known to predict MS risk at the time of first inciting event. There are no biologic markers that can distinguish multiple sclerosis from other demyelinating disorders.

Diagnostic Evaluation

Magnetic resonance imaging features of childhood MS are characterized by multiple white matter lesions. Pediatric patients tend to have less number but bigger lesions described as tumefactive lesions **(Fig. 2)**. This is due to the brief subclinical phase, immaturity of myelin system, and immunologic immaturity. In addition children may differ in their innate capacity for myelin repair leading to fundamental differences in the appearance of white matter lesions. This is particularly true for children with onset of MS before 10 years of age. Diffuse bilateral white matter lesions with ill-defined borders are common. Despite the dramatic appearance of the lesions, resolution of the initial lesions may be seen. The magnetic resonance imaging features of pediatric MS patients with onset above ten years often resemble that of adults with MS and is characterized by multiple, well-demarcated, homogenous small ovoid lesions often described as PPOL **(Fig. 3)**. The spinal cord lesions in MS tends to be located peripherally and typically involve short segments less than one vertebral body in length. The presence of hypointense lesions or *black holes* on T1-weighted MRI scans may indicate a chronic demyelinating process.

Different sets of magnetic resonance imaging criteria have been tested for their utility for diagnosis of multiple sclerosis in children and include 2010 Revised McDonald criteria, kids with multiple sclerosis (KIDMUS) criteria, and criteria proposed by Callen et al. and Verhey et al. The 2010 Revised McDonald criteria is currently being used to facilitate early diagnosis of MS in children based on adult studies. However, this has a less predictive value in the context of younger children and is not appropriate when there is an ADEM like presentation.

Intrathecal oligoclonal bands in the cerebrospinal fluid detected by isoelectric focusing are a feature of multiple sclerosis. Cerebrospinal fluid oligoclonal bands are reported in 72–84% of children with MS. Neurophysiological testing such as visual and auditory evoked potentials is also of diagnostic importance in detecting subclinical evidence of demyelination.

Treatment

All acute relapses of multiple sclerosis should be treated by intravenous corticosteroids. In contrast to ADEM, steroid taper in pediatric multiple sclerosis should be restricted to those patients with insufficient resolution of symptoms or those patients who experience symptoms after discontinuation of intravenous steroids and should be kept as short as possible. A second pulse of methyl prednisolone may be necessary in children with severe symptoms not responding sufficiently to the first course of corticosteroids. In case of fulminant demyelination plasma exchange should be considered timely.

Long-term disease modifying therapy Initiation of immuno-modulatory therapy is suggested in pediatric multiple sclerosis patients with active relapsing remitting disease as suggested by more than one clinical exacerbation/new/enhancing lesions on repeat MRI over a period of 2 years. The first-line drugs include interferon B and glatiramer acetate. Azathioprine is a secondary treatment option. The available literature on the use of interferon and glatiramer acetate in pediatric patients is restricted to tolerability data in isolated small case series or case reports.

NEUROMYELITIS OPTICA

Reports of NMO in children are sparse. Prospective studies report a relatively low frequency of pediatric NMO. A female preponderance is reported in NMO-IgG positive patients. Female-to-male ratio is near equal for the monophasic form.

Etiopathogenesis

Pathology of NMO is characterized by perivascular inflammation, often with infiltration of eosinophils and neutrophils as well as immunoglobulin and complement deposition. The serum autoantibody, aquaporin-4 (AQP4) antibody has been identified as a specific marker in patients with NMO. This antibody reacts with
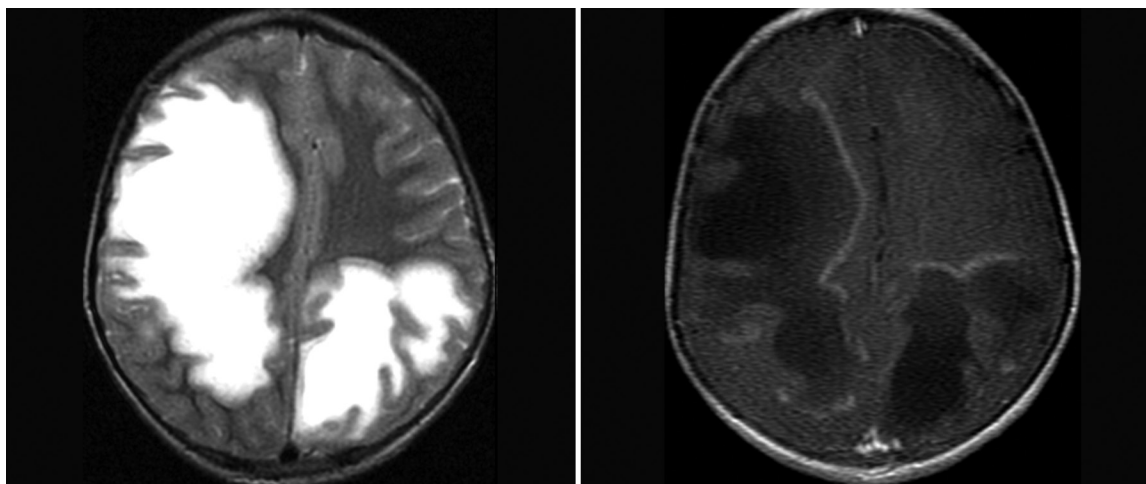
Figure 2 Tumefactive demyelination in a 7-year-old boy. Note the large white matter lesions resembling a tumor with open ring enhancement
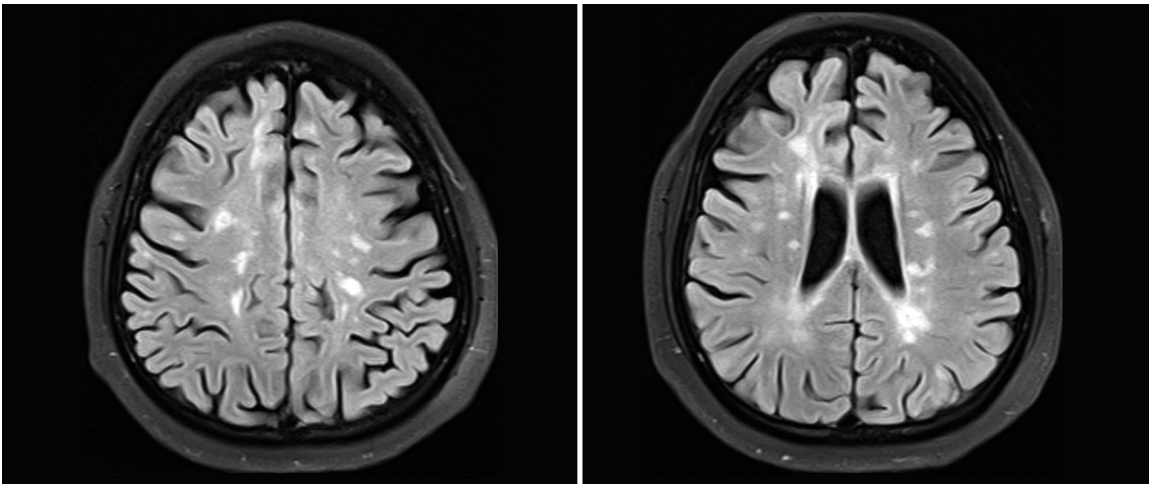
Figure 3 Brain magnetic resonance imaging shows discrete white matter lesions (periventricular perpendicular ovoid lesions) in a 14-year-old girl with relapsing remitting multiple sclerosis

the water channel protein AQP4 which is densely expressed in the astrocyte foot processes of astrocytes at the blood-brain barrier.

Clinical Features

Neuromyelitis optica is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Traditionally, the term NMO was applied to patients who experienced a monophasic event consisting of simultaneous optic neuritis and acute myelitis. Neuromyelitis optica spectrum is now recognized to typically evolve as a relapsing disorder and include patients with unilateral optic neuritis and myelitis occurring weeks or even years apart. A variety of extraneurological manifestations such as intractable vomiting, anorexia and weight loss have also been described as the presenting manifestation of these patients. These symptoms are attributed to the highly specific involvement of certain brain regions such as hypothalamus and medullary centers in these patients.

Magnetic resonance imaging may show signal intensity changes in the optic nerve with gadolinium enhancement. The spinal cord lesions are longitudinally extensive and involve more than three vertebral segments **(Fig. 4)**. The brain lesions in NMO are preferentially located at the sites of high aquaporin 4 expression such as hypothalamus and periventricular white matter. When occur, they are not oval or ovoid or perpendicularly located as in lesions of multiple sclerosis, but tend to be punctate small round dots. Few lesions can also be patchy and confluent. A cloud-like enhancement defined as multiple patchy enhancements with blurred margins in adjacent regions in contrast to the isolated spotty enhancement seen in multiple sclerosis may also help differentiating neuromyelitis optica from multiple sclerosis on imaging.

Cerebrospinal fluid examination includes a marked elevation in white cell count (often polymorphonuclear) in addition to elevated protein. In contrast to multiple sclerosis, only a small percentage of the patients show presence of oligoclonal bands.

Treatment

The first-line treatment for NMO is parenteral corticosteroids followed by oral steroids. Plasmapheresis should be initiated if a severe attack does not respond promptly to corticosteroids. This is especially important in cases of ascending cervical myelitis because

Figure 4 Spinal cord MRI (sagittal view) showing longitudinally extensive spinal cord lesions in a child with neuromyelitis optica

of the risk of neurogenic respiratory failure. Distinguishing NMO from multiple sclerosis in early stages is important. Seropositive patients with NMO may require long-term immunosuppressive therapy. Recent case reports and case series have shown that patients with NMO experience clinical deterioration under interferon-B treatment. It is shown that IFN-β treatment is not only ineffective for preventing relapses but also may increase the relapses significantly.

Prognosis of patients with NMO depends on presence of antiaquaporin antibodies. Seronegative patients with NMO usually have a monophasic course. Seropositive patients tend to have relapsing remitting course and the long-term prognosis is poor.

CLINICALLY ISOLATED SYNDROME

Clinically isolated syndrome refers to a first acute clinical episode of central nervous system symptoms with a presumed inflammatory demyelinating cause, for which there is no prior history of demyelinating event. The event is referred as monofocal if the clinical features are referable to a single central nervous

system site such as optic neuritis, transverse myelitis, brainstem, cerebellar or hemispheric lesions. Optic neuritis is defined by acute or subacute visual loss, restricted visual fields and pain with ocular movement. Transverse myelitis results in motor sensory or autonomic symptoms. A brief description of the clinical features and diagnostic evaluation in patients with acute transverse myelitis is given below. If the clinical features are characterized by signs and symptoms attributable to more than one central nervous system sites, the event is referred as polyfocal. The event should not include encephalopathy, though in brainstem syndromes encephalopathy may be present. The classification is purely based on clinical features rather than magnetic resonance imaging findings.

ACUTE TRANSVERSE MYELITIS

It is an acute inflammatory process affecting the spinal cord with relatively abrupt onset of motor, sensory and autonomic symptomatology. Even though most patients have a presumed postinfectious etiology, it can represent the sentinel event of a relapsing demyelinating disorder such as pediatric multiple sclerosis or NMO. It can also occur as an idiopathic monophasic illness. It is typically preceded by a mild illness in the 3 weeks prior to symptom onset, as reported in 50–100% of patients. The criteria for diagnosing transverse myelitis include sensory, motor, or bladder or bowel dysfunction attributable to the spinal cord, with progression to nadir in less than 21 days from onset. The clinical features depend on the location of the lesion. A high cervical cord lesion can present with acute respiratory failure. A sensory level may not be easily elicitable in the pediatric population. Initial evaluation should include a gadolinium-enhanced magnetic resonance imaging of the spine to exclude a compressive myelopathy. Magnetic resonance imaging usually shows hyperintense signal changes on T2W sequences. The extent of the lesions varies. Lesions of acute transverse myelitis in children are typically longitudinal, may demonstrate enhancement and are centrally located. If there is no evidence of a compressive lesion, a lumbar puncture should be performed. Cerebrospinal fluid typically shows pleocytosis and an elevated CSF IgG index. Other investigations recommended include parainfectious markers like virological serology. If there are features to suggest a systemic inflammatory disorder, autoimmune screening and serum angiotensin-converting enzyme levels are indicated. High-dose corticosteroids have shown to have beneficial effect and hasten recovery.

Differential Diagnosis

The differential diagnoses for a child who presents with an acute neurological deficit and white matter lesions on neuroimaging is wide. The features which should alert the clinician include the presence of fever, encephalopathy, involvement of the peripheral nervous system or other organ systems, absence of, or only minimal resolution of attack symptoms, a progressive disease course, elevated erythrocyte sedimentation rate (ESR) or leukocyte count, marked cerebrospinal fluid pleocytosis, and absence of isolated cerebrospinal fluid oligoclonal immunoglobulin G. Contrast enhancement may suggest an infectious, inflammatory or granulomatous disorder. Most often neuroimaging is the first available investigation and a critical look at the magnetic resonance image helps in formulating the differential diagnosis. The features to be looked are size and nature of the lesions (multifocal discrete, confluent or diffuse), topographical distribution of the lesion (predominantly white matter, basal ganglia, thalamus, brainstem, cerebellum) pattern of contrast enhancement (complete ring/ open ring/patchy/diffuse enhancement).

In tropical countries, infections of the central nervous system should be an important diagnostic consideration due to the therapeutic implications. Central nervous system infections that can present with white matter lesions include neurobrucellosis, neuroborreliosis, HIV encephalopathy and subacute sclerosing pan encephalitis. When there is complete ring enhancement of the lesions the differential diagnoses include brain abscess, tuberculoma and toxoplasmosis. When there is contrast enhancement, primary or secondary lymphoma also should be considered. Mutifocal discrete white matter lesions also may suggest primary or secondary central nervous system vasculitic disorders and noninfectious granulomatous disorders like neurosarcoidosis. Inherited disorders to be considered are leukodystrophies and mitochondrial disorders, especially when there is a progressive course.

Diagnostic Evaluation

In the absence of specific biological markers, diagnosis of acute demyelinating disorders is based on a combination of clinical, laboratory and magnetic resonance imaging features. All patients should be evaluated with neuroimaging preferably magnetic resonance imaging and cerebrospinal fluid testing. In the emergency setting a computerized tomogram (CT) of the brain may be necessary to rule out contraindication for a cerebrospinal fluid examination and to rule out other pathologies, especially if there is a delay in obtaining the magnetic resonance imaging. Magnetic resonance imaging of the brain and spinal cord with and without gadolinium should be obtained in all children with an initial demyelinating event. The work-up should also include cerebrospinal fluid studies including cell count with differential, total protein, IgG index, evidence of oligoclonal bands. The preferred method for detection of oligoclonal bands is the qualitative assessment of paired CSF and serum samples with isoelectric focusing. In addition to the routine testing, cerebrospinal fluid should be sent for infectious screening and virological studies, especially when the clinical features suggest an underlying infectious process. Other minimum tests include complete blood count with differential, ESR and antinuclear antibody testing. Expanded blood investigations depend on specific clinical situations. Neurophysiological testing such as visual evoked potentials, somatosensory evoked potentials and brainstem auditory evoked potentials is of additional diagnostic value. Evoked potential studies aid in localization of lesions and confirm organic basis for clinically ambiguous symptoms. Furthermore, evoked potential studies can identify clinically silent lesions, thereby providing objective support for dissemination in space in children with suspected multiple sclerosis.

A broad approach to diagnosis and classification in children with demyelinating disorders are shown in **Flow chart 1**.

IN A NUTSHELL

1. Central nervous system inflammatory demyelinating disorders comprise a group of disorders with heterogenous clinical manifestations.
2. It is important to distinguish monophasic demyelinating syndromes, such as ADEM from relapsing remitting disorders such as multiple sclerosis.
3. Diagnostic evaluation requires a careful exclusion of other similar disorders.
4. Early and correct diagnostic categorization in these children has prognostic and therapeutic implications.

Flow chart 1 Approach to diagnosis of acute demyelinating disorders
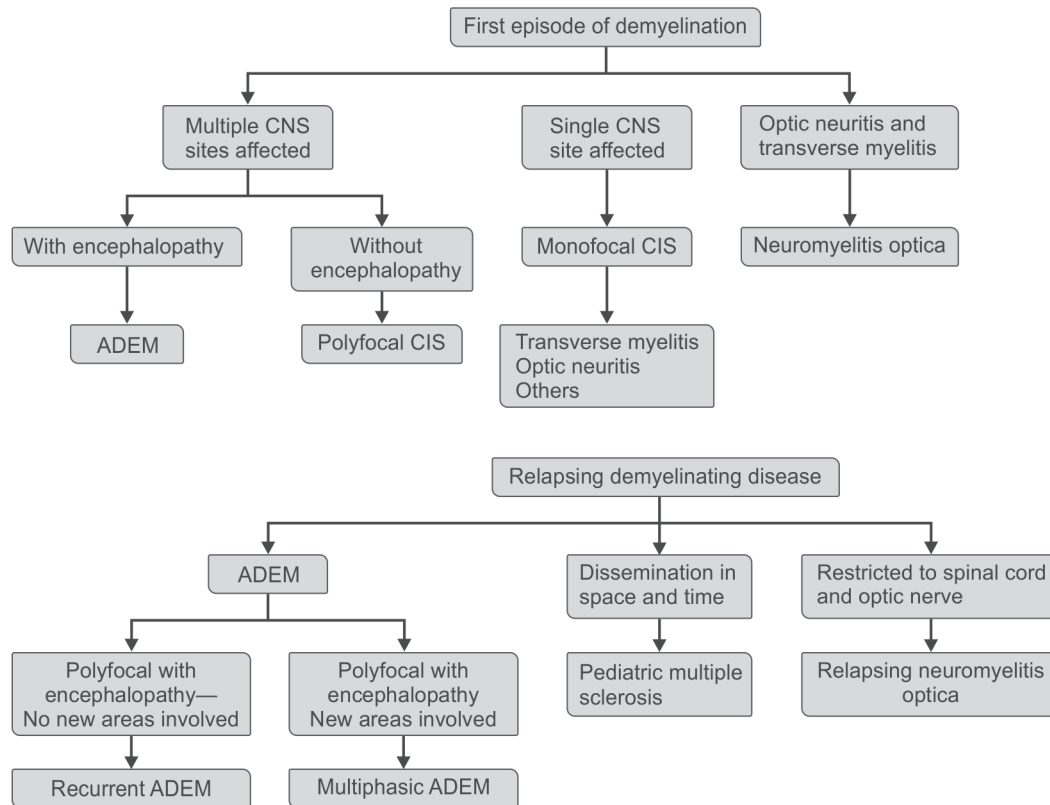
Abbreviations: CIS, clinically isolated syndrome; ADEM, acute disseminated incephalomyelitis; CNS, central nervous system.
[Adapted from Banwell et al. Lancet Neurology. 2011;10:436-45].

MORE ON THIS TOPIC

Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: comparison of presenting features. Dev Med Child Neurol. 2009;51:480-6.

Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol. 2011;10:436-45.

Banwell B, Shroff M, Ness JM, International Pediatric MS Study Group. MRI features of pediatric multiple sclerosis. Neurology. 2007;68 (16 Suppl 2):S46-53.

Callen DJ, Shroff MM, Branson HM, et al. Role of MRI in the differentiation of ADEM from MS in children. Neurology. 2009;72:968-73.

Hahn JS, Pohl D, Rensel M, et al. Differential diagnosis and evaluation in pediatric multiple sclerosis. Neurology. 2007;68:S13-22.

Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology. 2007;68:S7-12.

Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19:1261-7.

Mikaeloff Y, Moreau T, Debouverie M, et al. Interferon-beta treatment in patients with childhood-onset multiple sclerosis. J Pediatr. 2001;139:443-6.

Neuteboom RF, Boon M, Catsman Berrevoets CE, et al. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology. 2008;71:967-73.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292-302.

Wolf VL, Lupo PJ, Lotze TE. Pediatric acute transverse myelitis overview and differential diagnosis. J Child Neurol. 2012;27:1426-36.

Chapter 42.21

Autoimmune and Paraneoplastic Encephalitis and Encephalopathies

Lokesh Lingappa, Sirisharani Siddaiahgari

Encephalopathy in children and adolescents poses difficult diagnostic and therapeutic challenges. A study by the California Encephalitis Project, on the epidemiology and etiology of encephalitis, found that 63% of the patients remained without an etiology after a battery of tests for 16 potential infectious agents. The situation is much more difficult in the developing world in view of limited viral testing facilities. Most common cause in tropical or developing countries is still infection including viral, bacterial, rickettsial, tubercular or malaria. The differential diagnosis must include various noninfectious etiologies including drug-induced encephalopathy, vasculitis, metabolic encephalopathy and autoimmune encephalopathy. Though rare, malignancies can also present with encephalopathy as a presenting feature.

Antibody-mediated encephalopathy is a term used in children presenting with neurological syndrome associated with serum and/or cerebrospinal fluid (CSF) antibodies directed against ion channels, receptors and associated proteins. The clinical features of these disorders overlap and in many cases, the etiology may not be apparent at presentation. Investigation and treatment needs to be ongoing in this clinical situation.

The presenting manifestations vary and include, fever, seizures, amnesia, confusion, psychiatric features and encephalopathy with movement disorder in some. The encephalopathy can be part of a paraneoplastic syndrome. The presence of a tumor depends on the type of autoimmune disorder and gender. Nevertheless, the majority of children do not have any detectable tumor.

Autoimmune encephalitis **(Box 1)** are increasingly being diagnosed in children with antibodies against N-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel (VGKC)-complex proteins or other CNS antigens such as glutamic acid decarboxylase. The clinical phenotypes associated with

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BOX 1 Types of autoimmune encephalitis

1. N-methyl-D-aspartate receptor (anti-NMDA receptor antibody-mediated) encephalitis
2. Voltage-gated potassium channel related encephalitis
3. Hashimoto encephalopathy
4. Opsoclonus myoclonus syndrome

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these conditions are increasingly recognized **(Table 1)**. But some patients test negative for antibody tests available as of today.

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ENCEPHALITIS

N-methyl-D-aspartate receptor encephalitis is the most common autoimmune encephalitis in children worldwide. First described by Joseph Dalmau et al. in 2007, it is now being frequently diagnosed. Children constitute a large part of NMDA receptor encephalitis patients and tumors are present in less than 10% of patients in this age group, compared with 40–50% in women older than 18 years. In a study from UK, 23% of patients with NMDAR encephalitis were under the age of 18 years. Similarly, in a large US cohort, 40% of NMDAR antibody encephalitis presented in childhood or adolescence. Twenty-one percent of patients without a detected infection were found to have a specific antibody-mediated neurological syndrome in one retrospective study. In adults, the disease is commonly paraneoplastic, most frequently associated with ovarian teratoma. In children, associated tumors are rare.

Clinical Features

N-methyl-D-aspartate receptor encephalitis presents as a multistage encephalopathy including psychiatric manifestations, dyskinesias and occasionally limbic encephalitis (LE). Diagnostic criteria are summarized in **Box 2**. The phases of NMDAR encephalitis evolution are better delineated in adults than children. Fever is noted in the prodromal phase in many (phase 1). The various neurological manifestations include psychosis, confusion, amnesia, and dysphasia (phase 2). Some children are seen initially by psychiatrists. Symptoms progress to movement disorders, autonomic instability, hypoventilation, and often reduced consciousness (phase 3).

Choreoathetoid involuntary movements are characteristic, but some patients become mute and catatonic. The syndrome is characterized by severe motor disorder, perioral dyskinesias, and autonomic disturbances along with seizures. Fever is not a necessary presenting feature in these children. The perioral dyskinesias are the diagnostic abnormality which directs toward the diagnoses. This movement disorder is the key clinical feature in children that is characteristically early in onset, progressive in nature, unless intervened by immunomodulation in most.

Autonomic disturbances include brady- and tachyarrhythmias, rarely requiring cardiac pacing in children. Urinary disturbances like incontinence or retention are noted in few patients.

Recovery is often slow, even with immunotherapy and during recovery the clinical features tend to remit in the reverse sequence of their appearance. The symptoms will evolve in sequence, in some patients whereas in some, with less well-defined syndromes, symptoms can overlap, especially in those patients

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Table 1 Key features of important autoimmune neurological syndromes

Syndrome/ antibodies	Particular clinical features	Possible tumors	Immunotherapy response
NMDA receptor encephalitis/ NMDA receptor antibodies	Most common autoimmune encephalitis Seizures, psychosis, perioral dyskinesias, catatonia, autonomic disturbances, progressive course beyond 2 weeks after onset	Ovarian teratoma rare in preadolescent beyond 18 years—50%	Steroids, IVIG, plasmapheresis—rituximab, cyclophosphamide
Opsoclonus-myoclonus syndrome/ No defining Antibodies	Irritability, chaotic eye movements, myoclonus, ataxia and poor sleep	Neuroblastoma	ACTH, IVIG, rituximab
VGKC antibody related syndromes	Rare in children Psychosis, recent memory impairment, tonic seizures (faciobrachial seizures)	Non-neoplastic Occult neuroblastoma	Steroids, IVIG, plasmapheresis

BOX 2 Key features for diagnoses of NMDAR encephalitis

1. Psychiatric features
2. Memory disturbance
3. Speech disorder
4. Seizures
5. Dyskinesias
6. Decreased level of consciousness
7. Autonomic instability
8. Hypoventilation

N-methyl-D-aspartate receptor antibody encephalitis will have at least 3/8 of the above symptoms within 1 month of onset of disease.

Caution should be exercised in diagnosing anti-NMDA receptor encephalitis when patients after several weeks of disease onset develop only 1 or 2 of the above symptoms.

Figure 2 Postcontrast axial images demonstrating intense gyral enhancement in right occipitotemporal cortex

with psychogenic movement disorders, opsoclonus-myoclonus, or psychiatric syndromes.

Investigations

Magnetic resonance imaging of the brain often does not provide diagnostic information in this condition. The findings described include cortical (usually in the limbic mediotemporal cortex) or subcortical lesions in the brainstem or in the basal ganglia, or the cerebellum. T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities or contrast enhancement in cortical meninges or basal ganglia are detected **(Figs 1 and 2)**. MRI brain images are normal in more than 50% of cases.

The EEG may be abnormal at onset. Widespread interictal and ictal epileptiform activity arising from the cortex can be seen in some patients during the early stage of the disease. At later stages, generalized diffuse dysrhythmic high-amplitude slowing is seen. Extreme *delta brush* pattern is termed because of its resemblance to the delta brush (beta-delta complexes) pattern seen in premature infants, is seen in some children with anti-NMDAR encephalitis. CSF reveals moderate lymphocytic pleocytosis (median 32 cells per μL, range 5–480 cells per μL) at onset. Many may have completely normal CSF. Oligoclonal bands are detected in the CSF in later stage of illness. Viral polymerase chain reactions need to be performed in these children as they are most common differential diagnoses in this condition.

NMDAR antibodies These are detected both in serum and CSF with sensitivity in the CSF being marginally better than serum. Titers in

serum are higher than those in the CSF but when normalized to total IgG concentrations (which are about 300–400 times higher in the serum), almost all patients show high intrathecal synthesis of NMDAR antibodies. The persistence of antibodies for long period of time is noted in this condition and needs to be interpreted in conjunction with the clinical situation. Increasing titers on follow-up with clinical worsening is an indication for retreatment.

Differential Diagnosis

A high index of suspicion and awareness of the clinical phenotype is essential for appropriate diagnosis. The disorders with similar presentation which must be considered in the differential diagnosis include viral encephalitis, acute disseminated encephalomyelitis, central nervous system vasculitis and acute decompensation in inborn errors of metabolism.

Treatment

Studies have demonstrated clear clinical benefit in altering the course of the illness, if the treatment is started early. Patients with paraneoplastic etiology seem to have better outcomes than those with nonparaneoplastic disease particularly if they undergo tumor removal (and usually immunotherapy) within 4 months of presentation. Treatment regimes start with intravenous steroids followed by intravenous immunoglobulins. Many respond to these treatment options. Rituximab and cyclophosphamide are second-line medications, if children progress despite these medications. In many series, children respond to rituximab more often than first-line drugs. Cyclophosphamide subsequently, if required, seems to improve outcomes in resistant cases.

Outcome

The outcome of these patients is often good, but recovery can be slow and 15–25% of patients relapse. The recovery can take up to 2 years in these children and many come back to the baseline level of activities, especially those who are treated early in the course of illness.

Children without a tumor have increased risk of recurrence as compared to those with tumor. Presenting symptoms during relapse are similar to the initial presentation. Inadequate treatment of the first episodes, or occult tumors, might have been partly responsible for some relapses. Some fully recovered patients can still have detectable levels of antibodies in serum or CSF, suggesting a potential for reactivation of the immune response and clinical relapses in children with anti-NMDA receptor encephalitis.

Figure 1 Axial FLAIR MRI demonstrating hyperintensities in right occipitotemporal cortex

HASHIMOTO ENCEPHALOPATHY

Hashimoto encephalopathy is an ill-defined entity as the syndrome and immunological findings are unclear. There are less than 50 pediatric cases reported in the English literature. Hypothyroidism is seen in around 50% of affected children and rest are euthyroid; rarely few develop hyperthyroidism.

The clinical features include sleep and behavior abnormalities, stroke-like symptoms, tremor, myoclonus, transient aphasia, seizures, and ataxia. The MRI of the brain is usually normal. Cerebrospinal fluid protein level may be elevated. EEG studies show features of background slowing consistent with degree of encephalopathy. The thyroid function tests may be normal. The diagnostic investigation of this condition is detection of thyroid peroxidase antibodies (anti-TPO antibodies) along with a constellation of the clinical symptoms and response to corticosteroids.

The treatment of choice is steroids, about 50% of children respond to steroids. As in other autoimmune disorders plasma exchange or intravenous immunoglobulin have been effective in few cases.

VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODY-MEDIATED ENCEPHALITIS

Voltage-gated potassium channel antibody-associated LE was the first immunotherapy responsive neuronal surface antibody-associated CNS syndrome to be well characterized. It is extremely rare in pediatric age group (case series and reports) and has typical presentation with memory problems and seizures.

Antibodies to VGKC, GAD65, Hu, Ma2 have been reported in this clinical setting along with neuronal secreted protein called leucine-rich glioma-inactivated 1 (LGI1). These antibodies were previously thought to target the voltage-gated potassium channel. The current understanding is that LGI1 is a secreted neuronal protein that interacts with the presynaptic and postsynaptic proteins ADAM23 and ADAM22 that act to modulate synaptic transmission. The presenting features of patients with LGI1 include severe short-term memory loss, hyponatremia, and seizures, described as faciobrachial dystonic seizures or tonic seizures.

MRI evidence of medial temporal lobe inflammation is noted in approximately 60% of patients but pleocytosis or other CSF changes are uncommon, and oligoclonal bands are rare.

Treatment with intense immunotherapies has yielded good outcomes in about 70% of patients. Spontaneous improvements have been documented in some patients. A rarer condition associated with VGKC-complex is Morvan's syndrome, characterized by insomnia and psychosis, peripheral nerve hyperexcitability (including neuromyotonia and pain) and dysautonomic features. CASPR2-Abs are more common than LGI1-Abs in Morvan's syndrome. This condition is rarely seen in children.

RASMUSSEN ENCEPHALITIS

Rasmussen encephalitis is a constellation of features comprising a triad of refractory partial seizures, focal weakness (usually hemiparesis) and hemispheric atrophy. The etiology includes focal cortical dysplasias, gliosis secondary to perinatal injury and vascular malformation. When the initial neuroimaging does not reveal structural malformations, a possibility of autoimmune etiology is considered. This is an inflammatory encephalopathy characterized by progressive refractory partial seizures, cognitive deterioration, and focal deficits that occur with gradual atrophy of one brain hemisphere.

Children frequently present between 6 years and 8 years. Multiple theories have been proposed as there is no single etiological factor.

There is no clear explanation for unilateral involvement of brain in Rasmussen encephalitis. There is no diagnostic antibody testing for this condition. CSF is usually normal, and initial MRI is normal and later progress over period of weeks to months to develop progressive hemispheric atrophy.

High-dose methylprednisolone and intravenous immunoglobulin may be effective in early stages of disease. Rituximab and intraventricular alpha-interferon have been effective in a few isolated cases. The only definitive treatment is functional hemispherectomy that consists of surgical disconnection of the affected hemisphere.

OPSOCLONUS MYOCLONUS SYNDROME

Opsoclonus myoclonus syndrome (OMS) is a clinical constellation of evolving ataxia, opsoclonus with regression of speech or encephalopathy in presence of normal neuroimaging. Two to four percent of children with neuroblastoma develop OMS, which has a higher frequency of paraneoplastic syndrome than in most other cancers. OMS has a predilection for toddlers, and most cases are diagnosed before the age of 5 years as is the case with neuroblastoma.

The complete clinical syndrome may take time to evolve. Many of these, children present with isolated ataxia persisting beyond the first two weeks as seen classically in the postinfectious cerebellar ataxia. Opsoclonus is distinguished from nystagmus by its multidirectional, erratic, darting quality. The opsoclonus with irritability is a presenting manifestation in a proportion of children. Hence, a careful assessment of the abnormal eye movement along with pediatric ophthalmologist and verifying history of myoclonus or speech disturbances are helpful in making diagnoses. Myoclonus is subcortical in nature. It consists of muscle jerks of both small and larger amplitudes giving a tremulous appearance. They are action induced, but in severe cases, can be present at rest. Ataxia in OMS begins as gait ataxia, with falling and poor coordination, and progresses to include titubation and loss of ambulation. In rare situations, the tremors are so severe that all other manifestations may be masked precluding the accurate diagnoses.

Children with OMS are highly irritable and aggressive secondary to significant sleep disturbance. Cognitive impairment is noted in children with most severe course and multiple relapses. In these children, the IQ declines over a decade but then stabilizes later on. Other long-term behavioral issues include attention-deficit disorder and persistent rage but those are potentially treatable.

Investigation

Children presenting with ataxia need to have MRI brain performed to exclude other diagnosis. MRI of the brain is normal in OMS. All children with opsoclonus myoclonus syndrome need to be evaluated for presence of underlying neuroblastoma (Fig. 3). Routine CSF evaluation is normal in these children. Yield rate of spot urine vanillylmandelic acid (VMA) or 24-hour urine VMA analysis is poor.

High-resolution CT of chest, abdomen, and pelvis, carried out with oral contrast, probably has the highest yield. The size of tumor can be small in some children. If the CT is normal, a ^{131}I-metaiodobenzylguanidine (MIBG) scan is sensitive for neuroblastoma. If initial investigations are normal, these children should be screened every 6 months for up to 1 year from diagnoses of OMS.

Treatment

The current proposed treatment options include steroids (ACTH, dexamethasone), and/or IVIG. If the child is still encephalopathic
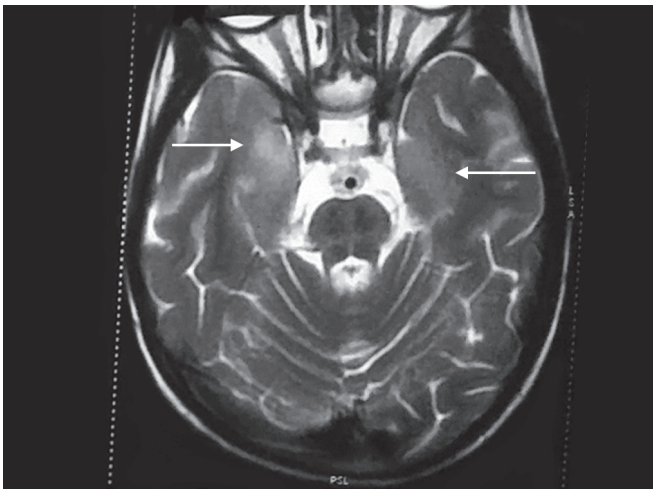
Figure 3 T2WI axial images—bilateral medial temporal signal changes noted in a child with neuroblastoma and limbic encephalitis

therapy to achieve complete remission along with prevention of relapses might help to reduce this long-term morbidity.

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IN A NUTSHELL

1. N-methyl-D-aspartate receptor antibody-mediated encephalitis is the most common autoimmune encephalitis in children.
2. N-methyl-D-aspartate receptor encephalitis is commonly paraneoplastic in adults, with ovarian teratoma being the most commonly associated tumor. In children, associated tumors are rare.
3. The characteristic clinical features of NMDAR encephalitis include seizures, psychosis, perioral dyskinesias, catatonia, autonomic disturbances, and progressive course beyond 2 weeks after onset.
4. The diagnosis is confirmed by the presence of NMDAR antibodies in the serum and CSF.
5. Treatment options include steroids, IVIG, plasmapheresis and in refractory cases rituximab.
6. Early treatment leads to a better clinical outcome.

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or nonambulant even 3 months into treatment, rituximab needs to be started early to improve the long-term outcome. Surgery is done in children with a tumor, and chemotherapy depending on the stage and complete or incomplete removal.

Prognosis

Factors predicting poor prognosis include infantile onset, loss of ability to walk or speak at onset, incomplete response to treatment, and multiple relapses. The course of OMS is not affected by presence or absence of a tumor. Relapses are noted in more than 50% of children. Majority are left with residual behavioral, language, and cognitive problems. An early and aggressive immunomodulatory

MORE ON THIS TOPIC

Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. Child Neurol. 2012;27:1460-9.

Brunklaus A, Pohl K, Zuberi SM, de Sousa C. Outcome and prognostic features in opsoclonus-myoclonus syndrome from infancy to adult life. Pediatrics. 2011;128;e388-94.

Pranzatelli MR, Tate ED. Opsoclonus-myoclonus syndrome. In: Dale RC, Vincent A. Inflammatory and Autoimmune Disorders of the Nervous System. Clinics in Developmental Medicine. Mc Kieth Press Book; 2010. pp. 184-5, 152-73.

Zuliani L, Graus F, Giometto B, et al. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. Neurol Neurosurg Psychiatry. 2012;83:638-45.

Chapter 42.22
Headache
Devendra Mishra

Headache is an extremely frequent occurrence in childhood and adolescence and is among one of the commonest reasons for a neurological consultation. The prevalence of primary headache ranges from 10% to 20% in school-aged children and increases with increasing age. Headache in a child may either represent a primary headache disorder such as migraine or tension-type headache (TTH), or may be a secondary headache due to an underlying neurological or non-neurological condition. Although validated diagnostic criteria for the diagnosis of headache disorders exist, the primacy for the pediatrician is to rule out serious underlying neurological disorder. History and clinical examination are the keys to headache management, with investigations infrequently required.

EPIDEMIOLOGY

Some geographical differences in the prevalence of headache and migraine are known, but the overall trend in occurrence is similar worldwide. Migraine is the third-most prevalent disorder and seventh-highest specific cause of disability worldwide. In a population based neuroepidemiological survey of more than one hundred-thousand individuals (34% < 15 years) in India in 2004, headache was the most frequent disorder diagnosed with prevalence rate of 1,119 per 100,000. Hospital-based studies among adults in India have reported migraine and TTH to be the most common headache disorders.

In an epidemiological survey of headache among 9,000 schoolchildren, one-third of the 7-year-old and half of 15-year-old children reported having at least one headache episode, thereby documenting for the first time, the high prevalence of headache in children. By age 15 years, around 5% of these children had experienced migraine. Migraine is reported to be common in males during prepubertal age but a well-established female preponderance is seen in adolescents and adults. The prevalence of migraine for children between 3 and 7 years is around 3%, and increases to 8% and 15% for those in the age-group 7–11 years and 11–15 years, respectively.

PATHOPHYSIOLOGY

Headache may arise from a variety of pain-sensitive structures, either intracranial (e.g., vascular sinuses, large vessels, dura surrounding these structures) or extracranial (e.g., skin, subcutaneous tissue, teeth). Although the brain, most of the dura, and ependymal are pain-insensitive; displacement, inflammation, injury or traction to the pain-sensitive structures may lead to a headache or facial pain. Most of the pain signals of head and face area are mediated through the trigeminal nerve and upper cervical nerves.

Migraine

Although recent research is advancing our knowledge of mechanisms of migraine, the exact pathophysiology remains unclear. A *trigeminovascular theory* is proposed. Migraine with aura is explained by a paroxysmal depolarization of cortical neurons. During the start of an attack, a *cortical spreading depression* (CSD) (a depression of spontaneous cortical electrical activity over the cerebral cortical surface) starts at the occipital pole of brain and moves anteriorly during the course of the attack at a rate of 2–3 mm/min. At the wavefront, neurons and glia depolarize, and there is also alteration of ion concentration between intracellular and extracellular compartments. These changes likely trigger the migraine aura and induce a reduction in posterior cerebral cortical blood flow. Multiple factors, including genetic predisposition, are proposed to be responsible for inducing the CSD. Cerebral ischemia is currently not considered to be important in the causation of migraine aura. The course followed by the CSD is independent of vascular territories and stops at the central sulcus.

The headache starts once the CSD reaches the pain-sensitive meningeal trigeminal fibers innervating the intracranial and dural blood vessels. The release of vasoactive substances such as substance-P and calcitonin gene-related peptide by the stimulation of trigeminal sensory neurons induces a neurogenic inflammation, which sensitizes the nerve fibers and leads to cutaneous allodynia. In migraine without aura, there are no demonstrable blood flow changes and mechanisms other than CSD are likely to be responsible, e.g., extracranial and intracranial arterial dilation.

Abnormalities in the metabolism and levels of various neurotransmitters, especially serotonin, have also been demonstrated in migraine. During an attack, the serotonin turnover decreases, whereas it is enhanced between attacks. 5-HT1, 5-HT2 and 5-HT3 are the serotonin receptors primarily involved in migraine pathophysiology. This also correlates with pharmacodynamics data as most drugs effective for acute management of migraine are agonists at the inhibitory 5-HT1_B and 5-HT1_D receptors, whereas propranolol and methysergide are antagonists to the excitatory 5-HT2 receptors.

Tension-type Headache

Previously considered to be primarily psychogenic, current research suggests a neurobiologic basis for TTH. The suggested mechanisms include genetics, muscle mechanisms, and central/peripheral pain sensitization. Peripheral pain mechanisms likely play a role in episodic TTH, whereas central mechanisms are more important in chronic TTH.

Genetics

Although familial occurrence of migraine is well-recognized, genetic studies do not support a Mendelian inheritance pattern for migraine. A high concordance rate among monozygotic twins in comparison to dizygotic twins has been reported, as has been the occurrence of similar subtype of migraine (with or without aura) among family members. Migraine thus appears to have a multifactorial inheritance probably leading to a genetic susceptibility. Familial hemiplegic migraine (FHM), a condition associated with prolonged neuro-deficit following a migraine headache, has shown a definite genetic inheritance pattern with subtypes described based on mutations in different genes viz., FHM1 with mutations in the *CACNA1A* gene (coding for a calcium channel) on chromosome 19; FHM2 with mutations in the *ATP1A2* gene (coding for a K/Na-ATPase) on chromosome 1; and FHM3 with mutations in the *SCN1A* gene (coding for a sodium channel) on chromosome 2.

Triggers

A number of intrinsic or extrinsic factors can trigger a migraine attack. The important triggers are stress, weather changes, fatigue, sleeplessness, hunger, and menstruation. Fasting has also been reported commonly as a trigger in Indian patients. Among Indian children, stress (both physical and emotional) and lack of sleep are the most common triggers.

Comorbid conditions Certain conditions occur commonly with headache and/or modify the headache characteristics. The more commonly recognized are obesity, epilepsy, sleep disturbances, allergy and sinus diseases, and psychological and emotional

disorders. Recognition of these conditions may help in deciding an appropriate therapeutic agent for headache (e.g., epilepsy, depression), and also assist in holistic management of the child.

CLINICAL FEATURES

Classification of the headache on the basis of temporal clinical pattern, as proposed by Rothner, is a useful clinical concept for initial evaluation. The five temporal patterns are: (1) Acute, (2) Acute recurrent, (3) Chronic progressive, (4) Chronic non-progressive, and (5) Mixed/comorbid headache. Each of these patterns suggests a distinct differential diagnosis.

Acute headache An acute headache in the neurologically normal child, although raising the possibility of serious intracranial pathology, is in the majority due to a viral infection such as upper respiratory tract infection or influenza. Migraine and serious neurological illness may also uncommonly present in this way. It can further be divided into generalized and localized headache. Acute localized headaches may be commonly due to sinusitis, dental pain, or temporomandibular joint dysfunction. However, in a febrile child with acute generalized headache, the need to rule out meningitis is paramount.

Acute recurrent headache It implies episodes of acute headache (irrespective of duration), separated by asymptomatic intervals, and is a pattern seen in migraine, TTH and cluster headache, though rare secondary causes such as intraventricular tumors (e.g., colloid cyst of the III ventricle) may present similarly. Majority of acute recurrent headaches in children presenting to a health setting are likely to be migraine.

Chronic progressive headache It is the pattern commonly associated with most of the serious intracranial diseases especially those with increased intracranial pressure, e.g., intracranial space occupying lesions, hydrocephalus, idiopathic intracranial hypertension. In a febrile child with such a history, chronic meningitis (especially tubercular) and brain abscess would be the important differentials.

Chronic nonprogressive headache It is a pattern of almost daily headache and usually a representation of chronic migraine. Other causes such as chronic sinusitis, ocular problems, hypertension, etc. may also need to be ruled out in this group.

Diagnosis of primary headache disorders of children rests principally on clinical criteria set forth by the International Headache Society (IHS), the International Classification of Headache Disorders, 3rd edition (ICHD-3). It is a comprehensive, predominantly evidence-based, hierarchical classification of headache disorders. An abbreviated form of this classification is provided in **Box 1**. The diagnostic criteria for children are not provided separately, although clarifications are provided, where appropriate. This classification system can be used both by the clinicians and the researcher, and brings much needed objectivity to headache diagnosis.

Migraine

Also called as common migraine, it is an acute recurrent type of headache disorder manifesting in attacks lasting 4–72 hours. Subtypes of migraine are listed in **Box 2**. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or vomiting, and both photophobia and phonophobia **(Box 3)**. Migraine with aura, also called classical migraine, occurs in 15–30% of pediatric migraineurs. It is characterized by transient focal neurological symptoms that usually precede or accompany the headache.

BOX 1 Classification of headache disorders as per ICHD-3

Primary headaches:
- Migraine
- Tension-type headache (TTH)
- Trigeminal autonomic cephalalgias (TACs)
- Other primary headache disorders

Secondary headaches:
- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder
- Headache attributed to nonvascular intracranial disorder
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
- Headache attributed to disorder of homeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- Headache attributed to psychiatric disorder

Painful cranial neuropathies, other facial pains and other headache disorders.

BOX 2 Subtypes of migraine

- Migraine without aura
- Migraine with aura
  - Migraine with typical aura
  - Migraine with brainstem aura
  - Hemiplegic migraine
  - Retinal migraine
- Chronic migraine
- Complications of migraine
  - Status migrainosus
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- Probable migraine
- Episodic syndromes that may be associated with migraine
  - Recurrent gastrointestinal disturbance
    - Cyclical vomiting syndrome
    - Abdominal migraine
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis

Migraine headaches in children and adolescents are commonly bilateral and mostly frontotemporal. The duration of headache is shorter than that in adults, and for diagnostic purposes a minimum duration of 2 hours is sufficient. It is also more frequently associated with emesis. Both types of migraine patients may also have a premonitory phase hours or days prior to headache and a resolution phase after the headache. Symptoms include hyperactivity or hypoactivity, depression, food-craving, and fatigue.

Episodic Syndromes Associated with Migraine

Also called childhood periodic syndromes, these include cyclical vomiting and abdominal migraine (together labeled as recurrent gastrointestinal disturbances), benign paroxysmal vertigo, and benign paroxysmal torticollis **(Box 4)**. These disorders occur either in persons who have an increased likelihood to develop or those who suffer from migraine. It is important to rule out posterior fossa tumors, seizures and vestibular disorders before making a diagnosis of benign paroxysmal vertigo. Abdominal migraine is characteristically not accompanied by headache during the episode, and a diligent search for a gastrointestinal disorder is necessary before making this diagnosis.

BOX 3 ICHD-3 diagnostic criteria for migraine

Migraine without aura:
a. At least five attacks[1] fulfilling criteria b–d
b. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)[2,3]
c. Headache has at least two of the following four characteristics:
   1. Unilateral location; 2. Pulsating quality; 3. Moderate or severe pain intensity; 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
d. During headache at least one of the following:
   1. Nausea and/or vomiting; 2. Photophobia and phonophobia
e. Not better accounted for by another ICHD-3 diagnosis

Migraine with aura:
a. At least two attacks fulfilling criteria (b) and (c)
b. One or more of the following fully reversible aura symptoms:
   1. Visual; 2. Sensory; 3. Speech and/or language; 4. Motor;
   5. Brainstem; 6. Retinal
c. At least two of the following four characteristics:
   1. At least one aura symptom spreads gradually over > 5 minutes, and/or two or more symptoms occur in succession; 2. Each individual aura symptom lasts 5–60 minutes;[4] 3. At least one aura symptom is unilateral;[5] 4. The aura is accompanied, or followed within 60 minutes, by headache
d. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

Note: [1]*Individuals who otherwise meet criteria for migraine without aura but have had fewer than five attacks, should be coded probable migraine without aura.*
[2]*When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.*
[3]*In children and adolescents (aged under 18 years), attacks may last 2–72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).*
[4]*When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 min. Motor symptoms may last up to 72 hours.*
[5]*Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.*

BOX 4 ICHD-3 diagnostic criteria for episodic syndromes that may be associated with migraine

Cyclic vomiting syndrome:
a. At least five attacks of intense nausea and vomiting, fulfilling criteria (b) and (c)
b. Stereotypical in the individual patient and recurring with predictable periodicity
c. All of the following:
   1. Nausea and vomiting occur at least 4 times per hour;
   2. Attacks last ≥1 hour and up to 10 days;
   3. Attacks occur ≥1 week apart
d. Complete freedom from symptoms between attacks
e. Not attributed to another disorder[1]

Abdominal migraine:
a. At least five attacks of abdominal pain, fulfilling criteria (b–d)
b. Pain has at least two of the following three characteristics:
   1. Midline location, periumbilical or poorly localized;
   2. Dull or *just sore* quality;
   3. Moderate or severe intensity
c. During attacks, at least two of the following:
   1. Anorexia; 2. Nausea; 3. Vomiting; 4. Pallor
d. Attacks last 2–72 hours when untreated or unsuccessfully treated
e. Complete freedom from symptoms between attacks
f. Not attributed to another disorder[2]

Benign paroxysmal vertigo:
a. At least five attacks fulfilling criteria (b) and (c)
b. Vertigo[3] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
c. At least one of the following associated symptoms or signs:
   1. Nystagmus; 2. Ataxia; 3. Vomiting; 4. Pallor; 5. Fearfulness
d. Normal neurological examination and audiometric and vestibular functions between attacks
e. Not attributed to another disorder

Note: [1]*In particular, history and physical examination do not show signs of gastrointestinal disease.*
[2]*In particular, history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.*
[3]*Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.*

Tension-type Headache

Previously used terms for this disorder were tension headache, muscle contraction headache, psychomyogenic headache, stress headache, psychogenic headache, etc. It is a common headache disorder with a life-time prevalence of more than 70%, and occurs in 10–25% children. It is characterized by infrequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild-to-moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present **(Box 5)**. The duration of headache in TTH is more variable and the pain is generally less severe than migraine.

Other Common Headaches

Chronic Daily Headache

Although not a standard diagnostic category, it is a commonly used clinical term. Chronic daily headache (CDH) is usually defined as headache occurring more than or equal to 15 days a month for more than or equal to 3 months. In children, it may be due to chronic migraine and/or TTH, new daily-persistent headache, or medication-overuse headache. Nearly 4% adults and 2% adolescents worldwide experience CDH. Around 1–5% children in school-based studies and around 25% in headache clinic-based studies are reported to have CDH. The importance of this condition is the frequent resistance to therapy, and the frequent occurrence of comorbid disorders including anxiety and depressive disorders, disorders of sleep, psychiatric disorders in the family, and other pain syndromes. Medication-overuse occurs concomitantly in about 30–35% adolescents with CDH.

BOX 5 ICHD-3 diagnostic criteria for tension-type headache*

a. At least 10 episodes of headache occurring on < 1 day/month on average (< 12 days/year) and fulfilling criteria (b-d)
b. Lasting from 30 min to 7 days
c. At least two of the following four characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
d. Both of the following:
   1. No nausea or vomiting
   2. No more than one of photophobia or phonophobia
e. Not better accounted for by another ICHD-3 diagnosis

*Note: *Headache occurring on 1–14 days/month on average for >3 months (≥12 and <180 days/year) with similar characteristics is labeled as frequent episodic tension-type headache.*

Post-traumatic Headache

Post-traumatic headache (PTH), a headache attributed to head and/or neck trauma, is the most common secondary headache with the prevalence of chronic PTH varying from 3.2% to 6.8% in children with head injury. It is defined as headache developing within seven days after head trauma (or after regaining

consciousness following head trauma) and resolving within 3 months or persisting beyond that time for being labeled as acute and persistent PTH, respectively. A late onset PTH starting after 7 days has also been described. The most common headache pattern is either episodic TTH or migraine without aura. Severity of head injury has not been found to correlate with severity or duration of PTH. Prognosis of PTH in pediatric population has been shown to be good with headache resolving over a variable period of time in majority. The pathophysiology of PTH is not well elucidated, though precipitation of primary headache in predisposed individuals is suggested.

APPROACH TO DIAGNOSIS

The crux of evaluation for a child with headache is a good history, which classifies the temporal pattern and guides to the likely diagnosis, and a thorough clinical examination that helps in ruling out underlying systemic diseases or neurological disorders as a cause of the headache **(Box 6)**. The history should be obtained directly from the adolescent patient, and with parental inputs in the younger patients.

Clinical Evaluation

History-taking in a child with headache is similar to that in any other disease, except for two caveats. It is difficult for children (even adolescents) to accurately describe the quality of pain, because of infrequent prior pain exposure and lack of appropriate vocabulary. Secondly, asking young children (<10 years) about the frequency or duration of headache is rarely going to provide reliable responses; parental reports should be used for confirmation. Many children with recurrent headache remain unclassifiable (or classified in probable categories) because of inability to communicate information regarding pain quality and severity, associated symptoms, and aggravation by activity. Thus, rigid adherence to diagnostic criteria may not be a beneficial approach in office practice.

Factors to be assessed in history include: onset, location and duration of headache, quality of pain, associated features (including aura and triggers), disability, school absences, drug history, family history, history of head injury, and comorbidities. Many drugs and food additives are known to cause migraine-like headaches, and need to be specifically ruled out. Common amongst these are analgesics (when over-used), carbamazepine, nitrites (present in cured meat), monosodium glutamate (MSG) in Chinese food, and caffeine. However, little published evidence is available for food items as the sole precipitants of headache, and should only be considered when each exposure leads to symptoms.

BOX 6 Red flags in headache evaluation

Symptoms:
• Chronic progressive headache
• Recent change in headache character or frequency
• Recent onset sudden severe headache (<1 month duration)
• Thunderclap headache
• Occipital location of headache
• Fever or increased temperature
• Retinal hemorrhages
• Neck rigidity
• Headaches accompanied by seizures

Signs:
• Fundal changes
• Abnormal neurological examination
• Gait abnormalities
• Altered sensorium

Caffeine intake may be evident (as with coffee/colas/tea) or unrecognized, in the form of carbonated drinks or energy drinks (many of which may not have a cola color but carry significant amounts of caffeine), and may cause a *caffeine-withdrawal headache*. The headache is usually a dull frontotemporal headache an hour or more after the last use. Treatment is by cessation of caffeine intake.

A detailed physical and neurological examination is crucial to exclude underlying disease processes. Fundus examination for papilledema may help to identify raised intracranial pressure, and is an important component. Blood pressure measurement with an appropriate-sized cuff is essential part of headache evaluation as underlying hypertension may be a cause of headache. A sudden rise in systolic BP causes explosive throbbing headache. Chronic hypertension may cause low-grade occipital headache on awakening that diminishes as the child gets up and begins activity, or frontal throbbing headache during the day. However, most children with chronic hypertension are asymptomatic.

Routine ophthalmological evaluation is unnecessary in recurrent acute headache, but may be indicated in a child with chronic headache who has never had an ophthalmological evaluation. If done, such an evaluation should include both refraction and an orthoptic evaluation. Dull aching pain behind the eyes that is quickly relieved when the eyes are closed, is usually seen in those with latent disturbance in convergence.

Routine ENT examination is also not indicated, unless recurrent acute headaches are coincidental with a viral syndrome, or localized headache is present with sinus tenderness. In case of frontal or maxillary sinusitis, tenderness is directly elicited over the sinus whereas with ethmoidal or sphenoidal sinusitis, deep midline pain behind the nose is characteristic. Radiological evidence of sinusitis should not be used to explain recurrent headaches, as sinusitis is not an uncommon finding during radiological examination for other diseases.

Pain Measurement

This is needed to determine, if treatment is necessary and to see the effect of treatment. Self-report is the most common measure of pain obtained from children, adolescents and adults. Children experience difficulty in describing pain using verbal language, but do better by matching with pictorial representation of emotions. Thus, asking children to match their experiences of pain with appropriate pictures of children's facial expressions are often used, e.g., Faces scale where children are asked to point to the face that best shows how much pain they are currently experiencing. The visual analogue scale (VAS) consists of a horizontal line, 100 mm in length which is anchored by word descriptors at each end. Marking occurs where current pain perception lies. VAS score is measured by measuring in millimeters from left hand end of the line to the point that the patient marks.

Headache diary The role of headache diary in pediatric pain conditions has a long tradition and significant evidence-base. A headache diary, maintained by the patient (with parental help in younger children), helps in documenting the headache duration, severity, associated factors, disability and medication-use. It also helps the child in taking control of his disease, and may help in objectively assessing the response to treatment.

Disability Assessment

Disability induced by migraine can be measured with question-naires developed and validated in migraine patients with good psychometric properties, such as MIDAS and HIT-6. WHO-DAS 2 is a general disability tool which was developed specifically for headache patients. PedMIDAS is a widely used tool to assess migraine disability in pediatric and adolescent patients. It has been

tested and validated for ages 4–18. It consists of seven questions for which scores are given based on the disability over the previous 3 months. Disability is graded into: No (score <11), mild (score 11–30), moderate (31–50), and severe (> 50) disability.

Investigations

Laboratory evaluation in a child with headache is guided by the clinical context; the plan of investigations will be different for a child with recurrent acute headache as compared to a clinically ill child being evaluated in the emergency room. For children with recurrent headaches, none of the routine hematological or biochemical studies has been found to be of any clinical utility. On the other hand, in a child with headache in association with features suggestive of an underlying neurologic or systemic condition, further laboratory studies may need to be ordered based on the suspected disorder. The EEG is not indicated for the evaluation of recurrent headaches. Similarly, CSF examination is also of limited value in the routine evaluation of headaches in children. However, it may be important when one is suspecting an underlying CNS infection or idiopathic intracranial hypertension.

Neuroimaging Around 15% children with recurrent headache are reported to have abnormalities on neuroimaging, though more than 80% of these are incidental or not requiring specific management. Most studies have shown that even though a significant minority of children with recurrent headaches has a surgically correctable lesion or medically amenable condition on neuroimaging, almost all had an abnormal neurological examination, e.g., papilledema, gait abnormalities, abnormal eye movement, etc. A practice parameter of the American Academy of Neurology also does not recommend neuroimaging in children with recurrent headache and a normal neurological examination. It may be considered when there is recent onset of severe headaches or when there is a change in the type or quality of the headache, and rarely if there is excessive parental concern.

MANAGEMENT

Management of headache encompasses both treatment of an acute attack and prevention of recurrence of further attacks. In addition, comorbidities need to be identified and managed, and biobehavioral interventions initiated to minimize the effects of the attacks. These therapeutic goals need to be shared with the patient and the family to ensure adherence to the management plan. The drugs used and the doses are detailed in **Table 1**. The hierarchy of management in the Indian setting should be home-based management with over-the-counter analgesics (and trigger avoidance), primary care-based management with prescription analgesics and common prophylactic drugs, specialist-supervised management with triptans and other prophylactic drugs.

Biobehavioral therapy or the incorporation of adherence, education, lifestyle adjustment, and coping skills is essential to the management of pediatric migraine. A regular and healthy lifestyle needs to be promoted including regular meals and a balanced diet (without meal-skipping), adequate hydration (and reduced intake of caffeine-containing beverages), regular exercises, sufficient sleep with regular sleep habits, and avoidance of triggers.

Migraine

Acute Treatment

Acute treatment aims at rapid and complete relief of headache and associated manifestations with early return to normal functioning. The drugs used fall in two categories, viz., nonspecific analgesics (acetaminophen and NSAIDs, especially ibuprofen) and migraine-specific agents (triptans). A practice parameter on management of pediatric migraine recommended ibuprofen as effective and paracetamol as probably effective for acute treatment. NSAIDs such as ibuprofen are effective when used in adequate doses early in the attack. In case of absence of complete response, triptans may be more effective. Triptans are 5-HT receptor agonists and the maximum pediatric experience is available for sumatriptan. In

Table 1 Commonly used drugs for management of migraine in children

Drug	Dose	Comments
Acute treatment (Avoid overuse of all acute medications)		
Paracetamol	15 mg/kg/dose, 6–8 hourly	Less effective than ibuprofen
Ibuprofen	7.5–10/mg/kg/dose, 8-hourly	
Triptans		Serotonin symptoms and vascular constriction (reduced somewhat with adequate hydration) are the main side effects
Sumatriptan	10 mg nasal, repeat once only after 2 hours, if needed 6 mg SC	
Almotriptan	12.5 mg	
Zolmitriptan	2.5 mg oral, 5 mg nasal	
Rizatriptan	5 mg (< 40 kg), 10 mg (≥ 40 kg)	
Prochlorperazine	0.15 mg/kg IV	More effective when combined with ketorolac and hydration
Preventive treatment		
Propranolol	2–3 mg/kg/day TDS	Begin at lower dose (~10 mg/day) and increase weekly, max dose 60 mg
Flunarizine	5–10 m/day HS	Start with 5 mg and increase in case of nonresponsiveness
Amitriptyline	1 mg/kg/day HS	Start at low dose, increase by 0.25 mg/kg every 2 weekly; initial side effects gradually subside
Cyproheptadine	0.2–0.4 mg/kg/day BD	Side effects reported less commonly in children
Antiepileptics		Usually half of epilepsy dose suffices
Sodium valproate	15–30 mg/kg/day, BD or TDS	Begin at 5 mg/kg/day, increase by 5 mg/kg 2-weekly
Topiramate	100–200 mg divided BD	Increase slowly over 3–4 months

Abbreviations: D, day; BD, twice-a-day; TDS, thrice-a-day; HS, single night-time dose; IV, intravenous; SC, subcutaneous injection.

the AAN practice parameter, among the triptans, only sumatriptan nasal spray was found to have sufficient evidence for acute management of migraine, and that too only in adolescents. The evidence in favor of subcutaneous or oral triptans was found to be insufficient. However, more data is now available on oral triptans and zolmitriptan, almotriptan, and rizatriptan have shown efficacy in pediatric migraine. Of these only almotriptan is FDA approved for children. Management of the migraine when above drugs fail and the child presents acutely to healthcare is not well-delineated. However, dopamine-antagonists (prochlorperazine) with intravenous NSAIDs may be effective. Intravenous dihydroergotamine may also be used for more severe cases.

To avoid medication overuse, nonspecific agents should be used less frequently than 2–3 times per week and triptans not more than 6 times per month. Use of other NSAIDs such as diclofenac or ketorolac can also be tried. Indomethacin has also been found useful, especially for stabbing headache and paroxysmal hemicranias, though the risk of side effects is higher. Domperidone (0.2 mg/kg/dose 8-hourly) or metoclopramide (0.1 mg/kg/dose 8-hourly) promote gastric emptying and normal peristalsis and may have some use in migraine with prominent vomiting, though pediatric evidence is not available. Compound preparations containing both analgesic and antiemetic (e.g., paracetamol and metoclopramide) are available for adults and convenient, but the relative dose of the individual drugs for pediatric patients is usually inappropriate. Combinations of two analgesics or codeine with paracetamol are available and used in adults, but not much information is available for children. Similarly, combining triptans and NSAIDs is effective in adults but pediatric data is lacking.

Preventive Treatment

Although no guidelines are available on when to start preventive therapy, it should be considered when migraine attacks are either too frequent (≥ 3/month) or too disabling (PedMIDAS score > 30, or causing frequent school absences). This decision needs to involve both the patient and the parents, and the goals (decrease headache frequency to < 1–2/month and disability to PedMIDAS score < 10) communicated to them. Preventive therapy should be used for a 4–6 month period before being gradually tapered, preferably at a time of low-stress, e.g., school breaks. Changing preventive therapy should be considered, if there is a lack of efficacy over a 6–12 week period, and/or unacceptable side effects appear. Quite a few drugs have been tried for preventive therapy but the following five are the most commonly used in pediatric patients (listed in a sequence of personal preference).

Among the antihypertensive agents, propranolol (a non-selective beta-blocker) and flunarizine (a calcium-channel blocker) are the two drugs commonly used in children. The longest clinical experience has been with propranolol, though high-class evidence for its efficacy is sketchy. However, used at 2–3 mg/kg/day in 2–3 doses, it has a good response. There is a need to rule out asthma and cardiac conduction disorders prior to starting the drug, and side effects include postural hypotension and depression. Children on beta-blockers should be cautioned against participation in competitive sports and rigorous physical activity. *Flunarizine* likely exerts its effect through selective inhibition of vasoactive substances on cerebrovascular smooth muscles. Drowsiness and weight-gain are the side effects, though once-a-day dosage is an advantage for school-going children. It was the only drug considered to be probably effective in the AAN practice parameter for treatment of migraine in children.

Although a variety of antidepressants are used for migraine prophylaxis, pediatric data for their use is lacking. The anti-depressant most frequently used in children for this purpose is *Amitriptyline*. Cardiac conduction abnormalities, sedation and anticholinergic side effects are the common problems with its use; a single-dose at bedtime is the preferred usage.

Cyproheptadine use in migraine prophylaxis, especially in children, has a long history. Good quality studies are lacking, but a dose of 2–8 mg/day at bedtime appears effective. The side effects of sedation and increased appetite are seen less frequently in children, as compared to adults. The utility of this agent is more for the management of cyclical vomiting syndrome, and also in migraineurs with prominent gastrointestinal symptoms.

As the pathophysiology of migraine has veered toward a primary neuronal initiation and a CSD, *antiepileptic drugs* are increasingly being evaluated and used as preventive therapy. Of these valproic acid and topiramate are the most commonly used in children, and also have reliable evidence of efficacy. Side effects of both these drugs are similar to those when used in epilepsy.

Other drugs like pizotifen, gabapentin, levetiracetam and clonidine have some evidences of efficacy and are in clinical use, but have not been detailed due to insufficient evidence, and infrequent use at our center. Nutraceuticals such as coenzyme Q_{10}, riboflavin and magnesium may have some roles in prophylaxis, but clear evidence of benefit is still awaited.

Tension-type Headache

Management of tension-type headache (TTH) in children suffers from lack of robust evidence for efficacy of various therapies. Due to the long duration and frequency of TTH, there is also a higher possibility of analgesic-overuse in this disorder. Moreover, psychosocial variables may too often be blamed as an etiological factor for TTH in children, probably a throwback to the *tension* headache days. However, if present, psychological factors need to be addressed.

Nonpharmacologic approaches such as biofeedback (either electromyographic or skin-temperature based), relaxation training, and psychological interventions have the benefit of avoiding or reducing pharmaceutical use and its related cost and side effect issues. However, availability of facilities and adherence to lifestyle management may be challenging.

Simple analgesics and NSAIDs are the first-line drugs for the acute management of TTH in children and adolescents. Since TTH is not associated with gastroparesis, these drugs might work better here than in migraine. Although the evidence for the utility of pharmacological preventive therapy in TTH in children is limited, the most widely used drug for this purpose is amitriptyline.

OUTCOME

Treatment of pediatric headache is generally effective, with most having improvement in headache characteristics, with more than 90% having sustained headache improvement as late as 5 years after appropriate diagnosis and management. Around two-thirds of migraine patients will have attacks throughout life, although a majority is intermittently free from them for long periods, or partially relieved with appropriate management. Our experience has been that after an appropriate diagnosis and detailed management plan has been made, majority of children evaluated for recurrent headache will require 2–3 additional visits, before the headache subsides or there is sufficient reduction in severity and disability so that home management suffices. Subsequent, follow-up visits can be on as needed basis or 6-monthly.

Parents of a child presenting with recurrent headache need both management of headache and also reassurance about absence of serious intracranial pathology. The cornerstone of evaluation in headache patient is history and physical examination, which occasionally aided by investigations, help in distinguishing primary and secondary headaches and initiating appropriate management. The role of a headache diary in the initial evaluation, and the need for a regular lifestyle during the management phase

needs to be recognized more widely. However, it should be remembered that only a minority of acute headache attending the emergency are due to serious intracranial conditions.

IN A NUTSHELL

1. Headaches are common in children and adolescents.
2. A good history and thorough examination is sufficient for accurate diagnosis in majority of children with recurrent headaches.
3. Routine eye examination or ENT work-up is not required for recurrent acute headaches.
4. A chronic progressive headache is an ominous sign and should be emergently evaluated.
5. Neuroimaging is infrequently required for headache evaluation.
6. Decide goals of management and communicate the same to the patient and parents.
7. Holistic management of primary headache should address lifestyle changes and avoidance of triggers, in addition to pharmacotherapy.

MORE ON THIS TOPIC

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2013;33:629-808.

Hershey AD. Current approaches to the diagnosis and management of paediatric migraine. Lancet Neurol. 2010;9:190-204.

Hershey AD, Powers SW, Vockell A, et al. Development of a questionnaire to assess disability of migraines in children. Neurology. 2001;57:2034-9.

Lewis DW, Ashwal S, Dahl G, et al. Evaluation of children and adolescents with recurrent headaches. Neurology. 2002;59;490-8.

Lewis D, Ashwal S, Hershey A, et al. Pharmacological Treatment of Migraine Headache in Children and Adolescents: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004;63;2215-24.

Mishra D, Sharma A, Juneja M, Singh K. Recurrent headache in pediatric outpatients at a public hospital in Delhi. Indian Pediatr. 2013;50:775-9.

Ravishankar K. Barriers to headache care in India and efforts to improve the situation. Lancet Neurol. 2004:3:564-8.

Rothner AD. Headache in children: A review. Headache. 1978;18:169-75.

Seshia SS, Wang SJ, Abu-Arafeh I, et al. Chronic daily headache in children and adolescents: a multi-faceted syndrome. Can J Neurol Sci. 2010;37:769-78.

Chapter 42.23
Movement Disorders
Debabrata Ghosh

Movement disorders comprise a group of heterogeneous conditions in which the primary symptom is a form of involuntary movement. In this chapter, primary focus is on the approach to the diagnosis and management of involuntary movements in children and brief discussion of some common disorders with involuntary movements. Based on the etiology, movement disorders may be classified as *Primary* (idiopathic or genetic), when there is no apparent structural brain abnormality on magnetic resonance imaging (MRI), or, *Secondary* (symptomatic), when there is a structural brain damage. For a complete evaluation of a child with a movement disorders, a 4-step system is followed:

- *Step 1:* Characterization of the 'abnormal involuntary movements'.
- *Step 2:* Associated neurological and/or systemic features.
- *Step 3:* Complete diagnosis of the *movement disorder*, comorbidities, and, etiology.
- *Step 4:* Management: medical and surgical.

Based on the type, movement disorders are divided into two basic categories: *hypokinetic* and *hyperkinetic*. Hyperkinetic disorders, manifest with either single or varying combination of *abnormal involuntary movements* such as dystonia, chorea, athetosis, ballism, tics, myoclonus, tremor, and stereotypy. Hypokinetic or bradykinetic (reduced movement) disorders are uncommon in childhood. Parkinson's disease and Parkinsonism, primarily adult disorders comprise the most of all cases of the hypokinetic or bradykinetic disorders. A few childhood movement disorders which may have Parkinsonian features include: a) early onset Parkinson's disease, b) Wilson disease, c) Juvenile Huntington disease, and d) Pantothenate kinase associated neurodegeneration (Hallervorden-Spatz disease).

The anatomical and physiological basis for the movement disorders and their pathogeneses are still not elucidated. Broadly stating, all movement disorders happen due to either structural or functional alteration in any of the anatomical structures comprising basal ganglia and/or its connection **(Fig. 1)**. Basal ganglia comprise of the following neuroanatomical structures—sensory or receptive or afferent limb: putamen, caudate nucleus (together called as striatum due to its striate appearance); efferent limb: globus pallidus, which is again divided into pars externa (GPe) and pars interna (GPi); substantia nigra, divided in two parts, pars compacta (neurons from here project to putamen), and pars reticulata (functionally an offshoot from GPi); subthalamic nucleus modulates the input to GPi. Thalamus, though not classically considered as part of the basal ganglia, but part of the thalamus forms an integral part of the corticostriatopallido-thalamic cortical circuit carrying the information from GPi to various areas of cortex. The basis for any of the involuntary movement lies in the dysfunction of the above circuit. There are multiple parallel pathways which subserve various specific functions still to be completely understood.

APPROACH TO MOVEMENT DISORDERS IN CHILDREN

In approaching a child with movement disorders the first step is a clear definition and understanding of the phenomenology of the underlying abnormal involuntary movements. Involuntary movements are not always describable, so observation of the movement is very vital to the diagnosis. Visual recognition through direct observation or review of the video recording is an excellent tool to supplement history from parents, caregivers and the patient him/herself. Home video is a good option, more so for the paroxysmal disorders. The event may not occur during the office visit. Patient's birth history, early development, previous illness, history of exposure to drugs and toxins, as well as social and family history are important. Description of semiology of the involuntary movements should include age of onset, course, types of movement, focality, timings, triggers, suppressibility, progression, and vocalization, impact of various activities on the involuntary movement and the impact of involuntary abnormal movements on various activities of life, sensory trick, self-stimulation, and self-mutilation. Changes in the movement in relation to awake/sleep state may give clue towards recognition of the involuntary movement. How the movement changes in supine, sitting, standing posture, and during walking may help in narrowing down the list of differential diagnoses.

The relationship of sleep and involuntary movements is very complex. Some of them may appear, some may persist, and some may disappear during sleep. Dystonia is a classic example of an involuntary movement which disappears during sleep. So the children with acute dystonic crisis are sedated for a shorter period to prevent muscle breakdown or severe pain/spasm/distress. **Box 1** shows a list of conditions associated with involuntary movements which occur or persist during sleep. For more detailed evaluation of these disorders, polysomnography may sometimes be indicated.

It is worthwhile again to reiterate that involuntary movements are merely physical symptoms/signs, not a diagnosis, and more often than not they do not occur always in pure form. A single disorder may have several types of involuntary movements of varying age of onset. Huntington's disease may produce akinetic rigid state in childhood but predominantly chorea in adults.
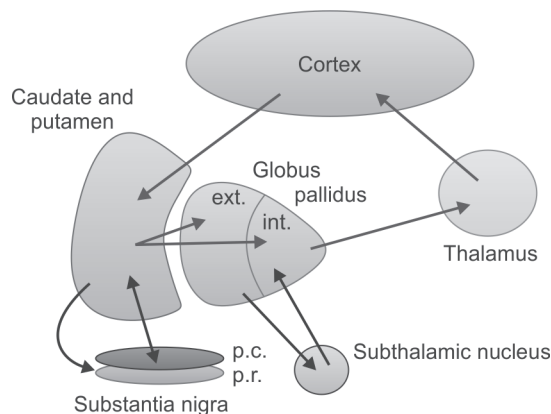
Figure 1 Basal ganglia anatomy and its connection forming multiple parallel *Cortico-Striato-Pallido-Thalamo-Cortical* circuits important for various abnormal involuntary movements
Abbreviations: ext, exterior; int, interior; p.c., pars compacta; p.r., pars reticulata

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BOX 1 Common abnormal involuntary movements in sleep

- Hypnic jerk (Benign nocturnal myoclonus)
- Bruxism (Tooth grinding)
- Rhythmic movement disorder
- Restless leg syndrome
- Palatal myoclonus/tremor
- Spinal myoclonus
- Paroxysmal hypnagogic dyskinesia
- Nocturnal myoclonic jerk associated with hyperekplexia.

Patients with dentatorubralpallidoluysiyan atrophy (DRPLA) may present with progressive myoclonic epilepsy with ataxia in a child and with chorea and dementia during adulthood. Primary myoclonus dystonia patients have both myoclonus and dystonia as the clinical feature. Symptomatic dystonia in children with cerebral palsy may coexist with spastic quadriparesis. There is also frequent co-occurrence of tremor or choreoathetoid movements in children with cerebral palsy. Symptomatic dystonia often manifests years after the inciting injury to the brain thus giving a false impression of another new onset disorder. The evaluating physician should bear this fact in mind when facing a situation when dystonia complicates the course of spastic quadriplegic cerebral palsy.

APPROACH FROM THE PERSPECTIVE OF ABNORMAL INVOLUNTARY MOVEMENT

There is paucity of data regarding prevalence of various types of abnormal involuntary movements in children. Personal observation of the author (2006–2009) in a tertiary care hospital in United States of America and the experience from another tertiary care center at Spain has been summarized in **Box 2**.

SPECIFIC ABNORMAL INVOLUNTARY MOVEMENTS

Dystonia

It is characterized by a forceful muscle contraction producing intermittent or sustained abnormal posturing or twisting of the body. It can be classified according to distribution in various body areas—focal (single body region such as tongue, hand, leg); segmental (involvement of a segment or region such as neck, face and neck, trunk, the whole limb); multifocal (multiple noncontiguous body areas), hemidystonia (one half of the body), and generalized (any focal and adjoining segmental or more body areas). Etiologically, dystonic disorders are classified broadly as

primary and secondary. In children, the most common primary dystonia is generalized, whereas in adults, focal/segmental. Common causes of dystonia in the pediatric age group are listed in **Table 1**. Paroxysmal abnormal involuntary movements are described separately.

Dystonia can be fixed or variable, and is often associated with irregular tremor, also called as dystonic tremor. The severity of dystonia is worse on attempted use of the affected body part(s), and it improves on rest. Dystonia nearly disappears during deep sleep. This fact is utilized in making the diagnosis of dystonia mimickers. If the posture or severity of the muscle contraction is unchanged or worse in sleep, the possibility of spasticity, contracture, psychogenic dystonia (not actual sleep), or dystonia as a manifestation of seizure, mostly of basal frontal origin, are more likely. The other characteristic feature of dystonia is co-contraction of agonist and antagonistic muscles, thus precise useful function is not possible. The muscle strength in primary dystonia is preserved; in fact individual muscles are stronger, and often work-hypertrophied. In spite of preserved strength of individual muscles, the precise control over the muscles is lacking. On attempted use of the limb for any purpose, the abnormal posture/twisting gets worse. The other feature of dystonia is overflow involving contiguous muscles, sometimes, there may be mass movement of the whole affected limb on attempted use of the limb. Anxiety/stress may bring on dystonia or may make dystonia worse, relaxation helps, as also sleep as mentioned earlier. The body or body parts may be so convoluted that the child may be curled up in bed all the time, unable to sit, stand, or walk. It may be difficult to use the wheelchair, dress/undress, put the shoes on, using orthotics. The persistent dystonic posturing may produce contracture and associated bony or joint changes. Dystonic muscles may be extremely painful as persistent involuntary muscle hyperactivity may increase the demand for oxygen or other metabolites, even normal blood flow may not be adequate thus there may be relative hypoxemia or metabolic insufficiency.

Dystonia, when generalized, severe, and progressive, and more so after a psychological or physical stress of infection or pain anywhere in the body, may be severe and persistent, not responding to the usual oral medication. This condition is then called as dystonic storm. During this storm, the child may have severe pain, and muscle breakdown producing rhabdomyolysis, and even renal failure. Dystonia is a well-known cause for elevated serum creatine phosphokinase (CPK). Dystonic storm has to be managed at a hospital, preferably at intensive care unit with sedation, hydration, monitoring renal and other systemic function, there may be a short-term need for general muscle relaxant and paralytic along with ventilation support.

BOX 2	Types of common abnormal involuntary movements in children	
	Alvarez, Aicardi 2001 **(n = 684)**	**Cleveland Clinic Series 2009** **(n = 434)**
Tics	39%	26%
Dystonia	24%	28%
Tremor	19%	8%
Stereotypy	0%	14%
Chorea	5%	8%
Myoclonus	2%	4%
Psychogenic	0%	5%
Ataxia	?	3%

Table 1 Common causes of dystonia in children

Congenital and developmental	Dystonic cerebral palsy, congenital brain malformation, basal ganglia stroke, benign dystonia of infancy, paroxysmal torticollis in infancy, dyspeptic dystonia with hiatus hernia
Infectious diseases	Viral encephalitis including Japanese B encephalitis, West Nile
Metabolic causes	Wilson disease, Dopa responsive dystonia, GM2 gangliosidosis, phenylketonuria (PKU), mitochondrial disease, glutaric aciduria, homocystinuria, tyrosinemia, neuronal ceroid lipofuscinosis, Lesch-Nyhan Syndrome
Medication/Toxin-induced	*Antipsychotic/Antiemetic:* Haloperidol, tetrabenazine, reserpine, phenothiazines, metoclopramide. *Antiepileptic:* Carbamazepine, phenytoin. *Toxic:* Methanol, carbon monoxide, manganese.
Hereditary/Degenerative disorders	Genetic dystonia (DYT 1,2,3,4,5,6,7,8,9,10,11; *DYT 1:* Torsin A mutation, *DYT 5:* Dopa responsive Dystonia, *DYT11:* Primary Myoclonus Dystonia), Rapid onset dystonia parkinsonism, pantothenate kinase associated Neurodegeneration (Neuronal brain iron accumulation—NBIA-1 or Hallervorden-Spatz disease); Ataxia telangiectasia, Huntington disease (Juvenile onset or Westphal variant), neuroacanthocytosis.
Psychogenic	Fixed, variable or episodic

Myoclonus

It is characterized by sudden shock-like forceful muscle contraction. Myoclonus may result from pathology in the cerebral cortex, subcortical region or spinal cord. Clinical evaluation should include the onset, time course, drug or toxin exposure, history of seizures, past and current medical problems, perinatal history, mental status changes, and family history. The neurological examination should include movement distribution, temporal profile, and activation characteristics. Distribution can be focal, multifocal, segmental or generalized. The temporal profile may be rhythmic (as in palatal myoclonus); irregular and unpredictable (as in propiospinal myoclonus). From the activation stand point, myoclonus may be at rest (spontaneous), or induced by various stimuli (reflex myoclonus), induced by voluntary movement (action myoclonus). Myoclonus is more often positive (muscle contraction), and rarely negative (loss of muscle tone/activity). The best example of negative myoclonus is asterixis, commonly noticed in diffuse encephalopathy due to advanced hepatic, renal, respiratory failures, or barbiturate poisoning. Etiologically, myoclonus can be classified into physiologic or pathologic.

Sleep myoclonus is a common physiological myoclonus. It happens mostly during early sleep, affecting any of the limbs, and sometimes even the whole body. Severity may vary from brief leg or arm jerk to whole body jerk. Sleep myoclonus is benign, usually starts during infancy and gets better in early childhood. The close differential is seizure, more so when it affects newborn babies. Video-EEG monitoring is commonly done to rule out seizures and thereby allay the anxiety among parents and pediatricians.

Pathologic myoclonus may be epileptic or nonepileptic. Epileptic myoclonus (i.e., myoclonic seizures, with epileptiform discharges on EEG) is a part of many epileptic syndromes (e.g., juvenile myoclonic epilepsy) and degenerative disorders (progressive myoclonic epilepsy); and is discussed in the chapter on seizures and epilepsy. Pathological nonepileptic myoclonus may further be classified as primary (myoclonus occurs as a primary symptom) and secondary (myoclonus occurs secondary to some other cause). Hyperekplexia is a form of nonepileptic myoclonus, which is stimulus sensitive, i.e., there is an exaggerated startle response. Any stimulus, tactile, auditory, or visual provokes an exaggerated startle with head flexion and extension and abduction of arms. The child may have frequent and persistent stiffening. **Table 2** shows common causes of pathological myoclonus in pediatric age group.

Myoclonus generally improves or disappears during sleep except the *palatal* and *segmental myoclonus*. This fact should be borne in mind to make a definitive diagnosis of the above. Palatal myoclonus in children is somewhat different from that in adults. There are two distinct variants of palatal myoclonus in children, one type, more common, is a developmental phenomenon noticed at about 4–5 years of life, this is usually benign and self-limiting with complete disappearance by the teen age years. The other variant is akin to that in adult, associated with hypertrophy of inferior olive, and persists throughout life with poor prognosis. Not uncommonly myoclonus may be psychogenic.

Chorea

This consists of irregular, unpredictable, brief, jerky, arrhythmic, semi-purposive movements that fleet randomly from one part of body to another. Chorea is characterized by or associated with hypotonia, *pronator sign* manifesting as pronation of forearm when arms are outstretched in front, motor impersistence manifesting as *milkmaid* grip, and *Jack in the box* tongue when asked to protrude the tongue out. Chorea also produces *hung up* ankle jerk due to superimposition of chorea during the elicitation of the deep tendon reflex. It may also cause *halted speech* due to superimposition of chorea involving the articulating muscles. There are several causes of chorea. Again the clinician must carefully consider the history, relation to preceding infection, exposure to medication, familial occurrence, age of onset and manner of progression. Hemichorea may result because of vascular causes. Benign hereditary chorea typically begins in childhood with a slow progression and very little or no cognitive change. Huntington's disease in adults is always associated with chorea, but presents with akinetic rigidity in children, usually with severe mental changes, seizures, and rapid progression. *Ballismus*, a forceful flinging movement, can be considered as violent chorea, with classic correlation with a lesion at subthalamic nucleus. *Athetosis* is the distal slow writhing, fluid, dancing type of movement, often associated with chorea. Athetosis can also be considered as distal dystonia affecting primarily the distal fingers/hands. Pseudoathetosis is a term used sometimes to describe involuntary movements mimicking athetosis but caused by the loss of proprioceptive input from the affected limb as is noticed sometimes in severe demyelinating polyneuropathy as a part of *deafferentation* syndrome when the brain does not get timely signal from periphery about the position of the limbs in space. **Table 3** summarizes common causes of chorea encountered in children.

Benign hereditary chorea may affect the child variably. Most of the affected individuals live normal life with minimal chorea which does not progress. The chorea is the only abnormality in

Table 2 Common causes of pathological myoclonus in pediatric age group

Primary	Essential myoclonus, primary myoclonus dystonia
Toxic	Lead, CO, mercury, toluene encephalopathy; tricyclics, lithium, selective serotonin reuptake inhibitor, monoamine oxidase inhibitors; antibiotics like penicillin, cephalosporins, quinolones; general anesthetics; anticancer drugs.
Traumatic	Intracerebral hemorrhage, subdural hematoma, diffuse axonal injury.
Vascular	Cerebral venous thrombosis; *Vasculitis:* Systemic or central nervous system.
Metabolic and endocrine	Hepatic failure, hypoxic encephalopathy, hypo- or hyperglycemia, hyponatremia, Wilson disease, uremia, mitochondrial encephalopathy, Gaucher disease, sialoidosis, gangliosidosis, neuronal ceroid lipofuscinosis (NCL), organic acidurias, urea cycle defect.
Degenerative	Lafora body disease, Huntington's disease, PKAN (Hallervorden-Spatz), Ramsay-Hunt syndrome, SSPE (Subacute sclerosing panencephalitis).
Infectious/ postinfectious	Meningitis, acute and chronic encephalitis, acute disseminated encephalomyelitis (ADEM), subacute sclerosing panencephalitis (SSPE).
Epileptic	Myoclonic epilepsies—Infantile, Juvenile; Progressive myoclonus epilepsies such as Unverricht-Lundborg disease, Lafora body disease.
Miscellaneous	Opsoclonus-Myoclonus, Palatal myoclonus, segmental myoclonus.

Table 3 Common etiologies of chorea in children

Congenital	Cerebral palsy (including kernicterus), birth trauma, congenital malformations
Genetic	Benign hereditary chorea, Fahr's disease, Friedreich ataxia, pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease), ataxia telangiectasia, Huntington disease, neuroacanthocytosis, Rett syndrome.
Metabolic	Wilson disease, mitochondrial disorders, Lesch-Nyhan syndrome, gangliosidosis, Neimann-Pick disease Type C, organic acidurias
Drug or toxin-induced	Neuroleptics including antiemetics, anticonvulsants, stimulants, isoniazid, carbon monoxide, oral contraceptives, Lithium, alcohol, propofol, tricyclic antidepressants, manganese.
Neoplastic	Brain tumors
Traumatic	Traumatic brain injury, burns encephalopathy in children
Systemic Condition	SLE, Henoch-Schönlein purpura, malnutrition, hypoglycemia, hypoparathyroidism, hyperthyroidism, Postopen heart surgery (Postpump chorea), chorea gravidarum.
Infectious	Post-streptococcal (Sydenham chorea), tubercular meningitis, neurosyphilis (congenital), viral encephalopathy, encephalitis, ADEM.

the affected child, behaves like static encephalopathy, many are misdiagnosed as cerebral palsy. It runs in family in an autosomal dominant fashion, there is mutation in the *NKX2.1* gene encoding for a homeobox protein. The course is usually benign, may not require any specific treatment. Avoiding the use of anticholinergic medication help these children as chorea can get worse with anticholinergics. Sydenham chorea is one of the common ones observed in developing countries and in some pockets in the developed as a part of rheumatic fever following a group A Streptococcal infection, primarily in the form of sore throat. Chorea usually appears after 4–6 weeks of acute streptococcal sore throat. Chorea may be the only manifestation of rheumatic fever as arthritis, carditis, and other major features may not be present any more by the time chorea appears. Presence of Sydenham chorea alone is an indication of putting the child on rheumatic fever prophylaxis; one does not need to wait for fulfillment of modified Jones diagnostic criteria. The chorea is accompanied by personality changes with anxiety, fidgetiness, and emotional liability. The symptomatic management of chorea in Sydenham chorea, if at all needed, is best achieved by the use of carbamazepine, haloperidol, valproate, or phenobarbital. The prognosis of chorea is excellent with near total disappearance over weeks to months. However, rheumatic fever prophylaxis with penicillin or other antibiotic (when penicillin sensitive) is mandatory as per standard recommendation.

Tremor

Tremor is characterized by regular rhythmic oscillatory movement of various body parts due to alternate agonist and antagonistic muscle contraction. The amplitude and speed of movement around the axis is the same in both directions of the movement. Behavior of tremor during physiological activity is important to find the etiology of the tremor. The distribution of tremor is also important. Rest tremor is best described as tremor at *repose*, typically starts when the affected body region is at rest, and goes away or at least gets significantly better on use of the limb. Typical example of the rest tremor is the one commonly observed in Parkinson disease or Parkinsonism. Usually, this type of tremor is slower, coarser, and it may occur in a pill rolling pattern. Tremor brought on with activity is called as action tremor. This tremor usually is faster, gets exaggerated on anxiety, does not change in frequency and amplitude in specific posture, or during specific targeted activity. This type of tremor is also called as exaggerated physiological tremor, rarely this produces significant dysfunction. However, recognition of this type of tremor may give a significant clue to some underlying serious but potentially treatable clinical conditions as mentioned in **Table 4**. The tremor which appears only before reaching a target, for example while doing finger nose

or heel to shin testing, is called intention tremor, alternatively termed as terminal tremor. Intention tremor is a cardinal feature of cerebellar dysfunction. This type of tremor is usually accompanied by ocular nystagmus, cerebellar dysarthria, and ataxia. Postural tremors are characterized by tremors in specific posture or during specific action. Essential tremor is a disorder, primarily characterized by tremor, which gets exacerbated in certain posture, such as outstretched arm, followed by hyperpronation of the forearm; bringing the fingers in front of the chest about to touch each other keeping the arms abducted at 90°, lifting arms above head and then full pronation or supination. The tremor of essential tremor also gets more prominent on useful activities such as holding a glass of water, pouring water from one glass to the other, using spoon, holding a piece of paper, handwriting, drawing a spiral, or line **(Fig. 2)**. Thus the tremor of essential tremor can also be considered as postural kinetic tremor. The other rare type of postural tremor seen primarily in adult is the orthostatic tremor, which starts abruptly when the affected person attains an upright posture, and the tremor involves lower body predominantly; this goes away when the person takes a few steps. This is one rare example of improvement of an involuntary movement on activity; most others get worse with activity.

Infantile Tremor Syndrome affects children between 5 months and 30 months of age, characterized by developmental regression, tremor, pallor, skin pigmentation, and discolored hair. This type of
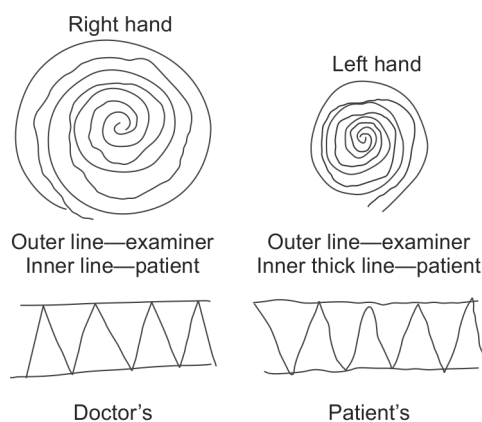
I enjoy playing soccer, my position in goalie.

Figure 2 Archimedes spiral drawing (inner line by patient) with either hand; line drawing, handwriting sample obtained from a 10-year-old boy with essential tremor

tremor, initially described only from Indian subcontinent, is now described from countries such as Iraq, Afghanistan, Myanmar, Somalia, Nigeria, and Turkey. The etiology is inconclusive, and most likely multifactorial. Theories are: a) *related to nutrition:* nutritional recovery from malnutrition to specific nutritional deficiency of vitamin B$_{12}$, magnesium, zinc; b) Infection-encephalitis; c) Metabolic deficiency of tyrosine metabolism, d) Toxic—still unidentified toxin from mother's breast milk. Tremor is noted in more than 95% cases affected; tremor starts abruptly in the upper limbs, later becomes generalized; intermittent to start with, later continuous; cry becomes tremulous. The tremor is usually coarse, 6–12 Hz, mostly action, and may have some rest tremor. Pretremor phase of the infantile tremor syndrome lasts for 2–12 weeks, tremor phase for an average of 6 weeks. On appropriate nutritional intervention, there is recovery in about 1–6 months. Rare mortality occurred due to intercurrent infections. Small studies have shown some persistence of subnormal cognitive abilities even after recovery from the illness. **Table 4** shows different types of tremor based on clinical characteristics and their causes.

Tics

These are brief, stereotyped semi-voluntary movements/jerks/posture/activity of various body parts, or production of a sound, associated usually with an urge, at least partially voluntarily suppressible, typically producing anxiety, if forced to suppress for a long time. Usually, the child can control them reasonably well at school or during the game, to be apparently released with more frequency or severity after coming back from school or after the game is over. Anxiety or stress may bring it on or make it worse. The course, typically, is fluctuating in childhood with periods (days to weeks) of worsening interrupted by periods (days to weeks) of improvement. There are two broad types of tics—motor, characterized by motor phenomenon, which may again be simple or complex. *Simple motor tic* is characterized by simple brief motor activity, whereas more complex movements are classified as *complex motor tic*, more so if, it mimics a physiological motor activity. The typical examples of simple motor tics are eye blinking, squinting, forceful eye gaze, opening of mouth, lip-smacking, head nodding, shoulder shrugging, facial grimacing, finger tapping, body jerking, stiffening of limbs. Examples of complex motor tics include combination of more than one of the above occurring concurrently, compulsive touching of the corners, touching of genitalia, obscene gestures, compulsive touching of others, skipping or jumping while walking, odd body postures while standing or walking.

The tic characterized by production of a *sound* is called vocal tic, which can be either *simple* or *complex* based on the simplicity of the sound. Vocal tics may be simple such as sniffing, throat clearing, grunting, tongue clicking, sighing, chirping, barking, or cough. Examples of complex tics are burping, hiccup, involuntary utterances of obscenities or swearing (coprolalia), repetitive utterances of words (echolalia, repeating other person's words and palilalia, repeating later portions of his own words).

Tic disorders are classified as *transient* tic disorder, if the tic symptoms resolve completely in 1 year; *chronic*, if lasts more than 12 months. Tourette syndrome is diagnosed, if multiple motor and at least one vocal tic persist continuously or intermittently for more than a year. Though Tourette syndrome is defined based on the presence of tics, the major management problem may stem from the comorbidity with this disorder, namely, attention deficit hyperactivity disorder (50%), obsessive compulsive symptoms (30%), obsessive compulsive disorders (30%), anxiety (5–10%), headache (up to 3/4th), sleep problem (60%), depression (5%). There is no unifying treatment for Tourette syndrome, and all the comorbidities are to be managed separately.

Stereotypy

Abnormal involuntary repetitive, stereotyped, patterned movements or vocalization, without changing patterns with time (tics change with time), usually time locked with excitement or boredom, may not be associated with any urge or compulsions. Unlike tics, the stereotypies last longer, as long as the inciting factor such as excitement continues. However, these movements stop, if attention is diverted. Usually, this starts before 2 years of age, much earlier than tics, which starts at about 6 years of age. As in tics, stereotypies are also classified as motor and vocal, and each as simple and complex. Some common examples of motor stereotypies are clapping, jumping, finger ringing, finger taping, piano playing movement with fingers, severe body or head rocking, twisting of limbs mimicking dystonia, complex body twisting and rhythmic body jerking or pelvic jerking. Examples of vocal stereotypies are hyperventilation, grunting or cooing sounds, mimicry, repeating the movie acts or dialogues. Stereotypies usually happen in the context of an underlying autistic spectrum disorder, communication problem, or a cognitively challenged state. These stereotypies are classified as secondary. About 5% of all stereotypies, however, happen in an apparently normally developing child with normal intellect and social skill. These stereotypies are classified as *primary*. Secondary stereotypies are more prolonged than primary, have more vocal and complex forms. Stereotype by itself is usually benign but its importance lies in the substrate in which this happens, for example, autistic spectrum disorders, or mental retardation, or communication problem.

DISORDERS WITH ABNORMAL INVOLUNTARY MOVEMENTS

Detail description of all the movement disorders in children is not possible in a single chapter. More emphasis is given on the disorders specific to the developing countries. Disorders with abnormal involuntary movements in pediatric age group can be broadly classified into four categories, which are:
1. *Development related:* The presence of motor phenomena that are considered normal during the developing period of life, self-limiting, improve or totally disappear on maturity.

Table 4 Different types of tremors in children

Variety	Causes
Rest tremor	Juvenile Parkinson disease, Wilson disease, drugs/toxins-like neuroleptics, manganese
Postural tremor	Essential tremor, Orthostatic tremor
Intention tremor	Cerebellar disorders, alcohol
Action tremor	Exaggerated physiological tremor—anxiety, hyperthyroidism, pheochromocytoma, hypoglycemia, drugs/toxins, e.g., stimulants, bronchodilators, valproate, lithium, mercury, arsenic, cyanide, cyclosporine, nicotine, selective serotonin reuptake inhibitors
Special types of tremor	Spasmus nutans, shuddering spells, jitteriness, Bobble-headed Doll syndrome, Infantile tremor syndrome, psychogenic tremor

2. Paroxysmal movement disorders.
3. Extrapyramidal disorders with primary (genetic/idiopathic) and secondary (hereditary/metabolic/other) known etiology (such as Wilson disease).
4. *Static encephalopathy*—producing chronic motor dysfunction (such as postkernicterus dystonia, mixed form of cerebral palsy).

Development-related Movement Disorders

Some abnormal movements are noticed during the stages of early development, but disappear later with maturation of the neuraxis. It is extremely important for a pediatrician to be familiar with these conditions as their prompt diagnosis will not only help lower the cost of unnecessary investigations, but also will allay the anxiety among the parents. Some examples include physiological infantile dystonia, physiological chorea of infancy, and benign neonatal and infantile myoclonus.

Extrapyramidal Disorders

Abnormal involuntary movements are quite common manifestations of neurometabolic/degenerative disorders. The details of the description of the extensive list of the diagnoses in this subgroup are out of the scope of this chapter due to the limitation of space. These are covered in the chapter on neurodegenerative disorders. A few important treatable conditions are discussed so as not to miss those diagnoses.

Wilson Disease

This diagnosis has to be considered in any child presenting with any acquired movement disorders. This is an autosomal recessive disorder secondary to mutation in the *ATP7B* gene encoding for copper transporting ATPase 2 protein responsible for transport of copper from liver to other parts of the body. Blood test for serum ceruloplasmin, copper level and eye examination for Kayser-Fleischer (KF) ring will confirm the diagnosis and is a must in every case of acquired movement disorders with onset after 3 years of age. Any type of involuntary movements such as dystonia, chorea, myoclonus, Parkinsonian features (bradykinesia, rigidity, tremor), cerebellar ataxia, cognitive/behavioral symptoms are the principal neurological target symptoms. Neurological involvement occurs typically after the earlier hepatic involvement. Copper chelation therapy using d-penicillamine or trientine is very useful, more so in combination with Zinc which prevents GI absorption of copper. The neurodeficit is largely reversible, if diagnosed and treated early. Liver transplantation is also promising as the last treatment option.

Myoclonus Dystonia

A combination of essential myoclonus and dystonia in an otherwise neurologically normal child with a normal MRI brain is very suggestive of this diagnosis. Epsilon-sarcoglycan (SGCE) mutation is the underlying genetic defect, but only about 50–70% cases may have this mutation. In suspected cases, a trial of trihexyphenidyl and/or clonazepam is very helpful. In selected cases, unresponsive to medication, deep brain stimulation of the bilateral globus pallidus pars interna is very effective.

Dopa Responsive Dystonia and Juvenile Parkinson Disease

Typically, the child with Dopa responsive dystonia has the following characteristics: 1) starts with dystonia affecting the legs asymmetrically; 2) diurnal variation with worsening during evening; 3) fatigability and improvement on rest or sleep; 4) normal cognition; 5) normal MRI brain. In such a case, it is

mandatory to try a levodopa-carbidopa combination. In a typical case of autosomal dominant type of Dopa responsive dystonia (Segawa disease), caused by a mutation of the *GCH1* gene coding for the enzyme, guanosine triphosphate (GTP) cyclohydrolase in the pterin pathway, the response to small dose of levodopa is dramatic and sustained without producing any side effect even when used over decades. If the diagnosis of Dopa responsive dystonia is suspected at whatever age, it is recommended to try levodopa so as not to miss this eminently treatable condition. A trial of levodopa should be instituted in any child with generalized dystonia as the first medication. Other medications for dystonia are tried only after adequate trial with levodopa-carbidopa has been completed. Juvenile Parkinson disease may complicate the course of Dopa responsive dystonia, if untreated. The typical features of Parkinson disease in the form of bradykinesia, rigidity, rest tremor are present in this condition. When this condition occurs due to genetic defects other than the one associated with Dopa responsive dystonia, the treatment response may not be that encouraging and there may be a lot of dyskinesia or dystonia complicating the clinical scenario.

Investigations in Pediatric Movement Disorders

The following are the common investigations undertaken for evaluation of movement disorder in children: magnetic resonance imaging (MRI) of the brain, biochemical analysis of blood/urine/CSF, neurophysiology, and genetic study, in selected cases.

TREATMENT OF PEDIATRIC MOVEMENT DISORDER

Dopa Responsive Dystonia and Juvenile Parkinson Disease

Levodopa-carbidopa (4:1): 1–5 mg/kg/day (calculated on levodopa content), to be taken without protein food; 100% response, no side effect, if the diagnosis of Dopa responsive dystonia is correct.

Other Dystonias

The medical treatment response is not much encouraging. Following medications are often tried on a trial and error basis:

- *Anticholinergics:* Trihexyphenidyl, benztropine useful in about two-thirds of cases; limiting side effects are cognitive/behavioral and constipation.
- Benzodiazepines including baclofen, clonazepam useful in about 60% cases.
- Dopamine receptor blockers may help in up to 50% cases; may have dyskinetic side effects.
- *Tetrabenazine:* Dual action with dopamine depletion and receptor blocking with less dyskinetic side effects, may help in recalcitrant cases.
- *Drug-induced dystonia:* Anticholinergics such as benadryl, trihexyphenidyl, benztropine; the response is excellent with any of them.

Tardive Dyskinesia

Uncommon in children; in case this happens, stop or lower the dose of the offending medication; anticholinergics and tetrabenazine are tried with some success.

Tremors

Essential tremor Propranolol, primidone, topiramate useful in about two-thirds cases for each.

Rest tremor Responds well to levodopa-carbidopa or Dopa agonists such as ropinirole, pramipexole.

Myoclonus

Antiepileptics such as valproate, zonisamide, levetiracetam, clonazepam; most effective for epileptic myoclonus.

- *Piracetam or 5-hydroxytryptophan:* Hypoxic myoclonus.
- Tetrabenazine tried with variable success in other cases.

Tics

Clonidine or guanfacine for tics of modest severity, also helps comorbid hyperactivity; typical antipsychotic such as haloperidol, pimozide for more severe cases; atypical antipsychotics such as risperidone, aripiprazole, olanzapine, quetiapine. Tetrabenazine is also tried with some success.

Chorea/Athetosis/Ballismus

Dopamine antagonists including pimozide, haloperidol, tetrabenazine; anticonvulsants: carbamazepine, valproate, carbamazepine, phenobarbital. Avoid use of anticholinergics as they worsen chorea or athetosis.

Myoclonus dystonia Trihexyphenidyl and clonazepam are very useful.

Hyperekplexia Clonazepam is helpful.

Surgical Management

Deep Brain Stimulation

Bilateral globus pallidum pars interna (GPi) very effective in primary dystonia in children with more than 90% persistent symptom relief. The response in secondary cases is not that encouraging, only about 33% response rate in that subgroup. Myoclonus dystonia also responds to deep brain stimulation (DBS). Some cases of severe form of Tourette syndrome also benefit from this surgical management.

Thalamic ventral intermediate nucleus Excellent response in essential tremor, though rarely needed in childhood; helpful in some other pharmacoresistant tremors of any type.

Subthalamic nucleus in severe cases of juvenile Parkinson disease, posterior subthalamic area in essential tremor.

Extirpative Surgery

Pallidotomy or thalamotomy—effective, but as these are irreversible procedures, they are currently being replaced by deep brain stimulation in the developed countries. These procedures still have a role in resource-poor developing countries.

IN A NUTSHELL

1. Movement disorders are divided into two basic categories: *hypokinetic* and *hyperkinetic*.
2. Hyperkinetic disorders manifest with either single or varying combination of "abnormal involuntary movements" such as dystonia, chorea, athetosis, ballism, tics, myoclonus, tremor, and stereotypy.
3. Hypokinetic disorders are uncommon in childhood. A few childhood movement disorders which may have Parkinsonian features include early onset Parkinson's disease, Wilson disease, Juvenile Huntington disease, and Hallervorden-Spatz disease.
4. Disorders with abnormal involuntary movements are classified into four categories: development related; paroxysmal movement disorders; extrapyramidal disorders; and static encephalopathy.
5. MRI of the brain, biochemical analysis of blood/urine/CSF, neurophysiology, and genetic studies are the common investigations undertaken for evaluation of movement disorders.
6. Both medical and surgical treatments are available.

MORE ON THIS TOPIC

Elias WJ, Shah BB. Tremor. JAMA. 2014;311:948-54.

Ghosh D, Indulkar S. Primary Myoclonus-Dystonia: a diagnosis often missed in children. J Child Neurol. 2013;28:1418-22.

Ghosh D, Rajan PV, Erenberg G. A comparative study of primary and secondary stereotypies. J Child Neurol. 2013;28:1562-68.

Ghosh D, Sreshta S, Velayudam K. A study of chorea in children (Abstract). Dev Med Child Neurol. 2013;55(Suppl 3):59.

Ghosh P, Machado A, Deogaonkar M, Ghosh D. Deep brain stimulation in children with dystonia: Experience from a tertiary care center. Pediatr Neurosurg. 2012;48:146-51.

Kahn E, Falcke HC. A syndrome simulating encephalitis affecting children recovering from malnutrition (Kwashiorkor). J Pediatr. 1956;49:37-45.

Malaty IA, Akbar U. Updates in medical and surgical therapies for Tourette Syndrome. Curr Neurol Neurosc Rep. 2014;14:458.

Morgante F, Klein C. Dystonia. Continuum. 2013;19:1225-41.

Rajput AH, Adler CH, Shill HA, Rajput A. Essential tremor is not a neurodegenerative disease. Neurodegen Dis Manag. 2012;2:259-68.

Walia BNS, Ghosh D. Infantile Tremor Syndrome. In Neurology in Tropics, JS Chopra, IMS Sawhney. New Delhi: BI Churchill Livingstone; 1999.pp.512-23.

Chapter 42.24
Childhood Ataxia
Asuri N Prasad

Ataxia is defined as an inability to maintain normal posture and smoothness of movement. Additional neurological problems such as seizures and movement disorders (e.g., dystonia, chorea) may accompany ataxia. Consequently, many variations are encountered in the clinical phenotype, ranging from findings of pure cerebellar dysfunction to mixed patterns of involvement reflecting extrapyramidal pathways, brainstem, and cerebral cortical involvement. To consider the entire gamut of diseases that can lead to ataxia as a symptom in children would be beyond the scope of this chapter. However, the reader will be able to develop a clinical approach based on the information provided in this discussion and select suitable laboratory tests that would help confirm a diagnosis. Clearly, treatment options may have to be individualized, and as outcomes are dependent on the nature of the underlying condition and its natural history.

CEREBELLAR FUNCTION

Principal cerebellar functions involve control and modulation of locomotion, postural control, voluntary movements, and rarely cognition. Lesions of the midline cerebellar vermis produce truncal and gait ataxia, while involvement of the lateral cerebellar hemispheres produces a picture dominated by limb ataxia. Interruption of afferent and efferent connections within the neocerebellar system results in an ataxic gait (i.e., swaying in the standing posture, staggering while walking, with a tendency to fall and the adoption of a compensatory wide base), scanning dysarthria, explosive speech, hypotonia, intention tremor (i.e., oscillation of limbs that is pronounced at the end of a planned movement), dysdiadochokinesia (i.e., impaired alternating movements), dysmetria (i.e., impaired judgment of distance), decomposition of movement, and abnormalities of eye movements (i.e., nystagmus).

EPIDEMIOLOGY

The prevalence of childhood ataxia varies by region, and by etiology. A prevalence rate of almost 26/100,000 children in Europe was reported in a recent systematic meta-analysis of published data on childhood ataxia. The causes of ataxia vary depending on the methodology adopted. A study looking at pediatric chronic ataxia relied on a database search at a tertiary care referral center in Canada came up with annual crude incidence rate of 3.1 per 100,000 and a crude period prevalence rate of 6.62 per 100,000. Overall, it is likely that the prevalence and incidence of ataxia is significantly underestimated.

ETIOLOGY

Box 1 lists the causes of acute ataxia in children. The etiologies are varied, involving; parainfectious, toxic-metabolic, vascular/ischemia, immune-mediated inflammation, trauma, tumors, paraneoplastic conditions. As such postinfectious, immune-mediated inflammatory conditions, as well as posterior fossa tumors are important considerations and are encountered quite frequently.

Chronic pediatric ataxias have structural, genetic and metabolic causes. A classification system has been developed on the basis of presentation and progression, involvement of multiple systems, and more specific symptoms such as epilepsy. Under each broad category, the mode of genetic inheritance is used as a basis to further categorize conditions and include traditional as well as nontraditional modes of inheritance (maternal inheritance, triplet repeat disorders, imprinting disorders, etc.) **(Box 2)**.

ACUTE ATAXIA

The presentation is usually striking and represents an acute change from a normal neurological baseline. The features are of a cerebellar syndrome with ataxic gait being a primary feature in midline lesions, and in toxic metabolic etiologies. Asymmetry and lateralization of abnormalities in terms of coordination, limb ataxia, and lurching to one side may be seen with unilateral lesions

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BOX 1 Causes of acute ataxia in childhood

- *Postinfectious:* Varicella, Epstein-Barr, enterovirus
- Toxic-drug induced
- Tumor-posterior fossa
- Hydrocephalus
- Acute demyelinating encephalomyelitis
- Basilar migraine/migraine equivalents
- Posterior circulation strokes
- Neuroblastoma-associated opsoclonus-myoclonus-ataxia
- Benign paroxysmal vertigo
- Guillain-Barré syndrome and the Miller-Fisher Variant

BOX 2 Classification of ataxia using a genetic-biochemical basis

Nonprogressive ataxias:
- Pure congenital cerebellar ataxias with or without cerebellar hypoplasia
  - Autosomal recessive
  - Autosomal dominant
  - X-linked
  - Unknown
- With posterior fossa malformations—autosomal recessive (e.g., Dandy-Walker syndrome)
- *Congenital ataxia syndromes with cerebellar malformations:*
  - Autosomal recessive (e.g., Joubert syndrome)
  - X-linked recessive (e.g., X-linked congenital cerebellar hypoplasia and external ophthalmoplegia)

Intermittent/episodic ataxias:
- Autosomal dominant—channelopathies [e.g., episodic ataxias (EA) 1, EA 2]
- Autosomal recessive—enzyme defects [e.g., maple syrup urine disease (MSUD), urea cycle defects]
- X-linked—enzyme defects [e.g., ornithine transcarbamylase (OTC) deficiency]

Progressive ataxias with or without multisystem involvement:
- Autosomal dominant—ataxias with spinocerebellar dysfunction, triplet repeat disorders [e.g., SCA 1-23, dentatorubropallidoluysian atrophy (DRPLA)]
- Autosomal recessive
  - Ataxias with spinocerebellar dysfunction, triplet repeat disorders (e.g., Friedreich ataxia)
  - Impaired DNA repair mechanisms (e.g., Ataxia telengiectasia)
  - Enzyme defects (e.g., Refsum disease)
- Maternal inheritance—Mitochondrial disorders (e.g., MERRF)

Ataxias with polymyoclonus and seizures:
- Autosomal recessive
  - Dodecamer repeat expansions (e.g., Lafora body disease)
  - Enzyme defects (e.g., neuronal ceroid lipofuscinosis)
- Maternal inheritance—Mitochondrial cytopathies [e.g., myoclonic epilepsy with ragged-red fiber disease (MERRF), mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS)]

Other:
- Angelman syndrome
- Fragile X-related ataxia/tremor

of the cerebellum and brainstem connections. There may be other features such as nystagmus, pyramidal and extrapyramidal features, and involvement of higher cerebral functions depending on etiology.

Approach to a Patient with Acute Ataxia

The process of evaluation depends on important data elements collected through history, and examination findings. Information on exposure to infections, a prodromal illness, vaccinations, trauma, medications, toxins are of vital importance. Associated symptoms of headache, signs of raised intracranial pressure may point towards the presence of an intracranial lesion such as a tumor. Examination findings may be particularly significant in picking up on signs of cerebellar dysfunction as well as involvement of extrapyramidal pathways (dystonia). Presence of hyper-reflexia and spasticity points to an upper motor neuron involvement. Associated areflexia and motor weakness suggest Guillain-Barré syndrome as likely etiology. Signs of vestibular dysfunction elicited by a Dix-Hallpike maneuver may confirm a peripheral sensory contribution to the symptoms of ataxia.

Laboratory investigations should include; drug and toxicology screen, neuroimaging studies, lumbar puncture and CSF analysis (lactate, protein, oligoclonal banding, antibody screens for viral studies) can provide specific clues to inflammatory, demyelination, and the presence of intracranial pathology. Nerve conduction and electromyography may show a conduction block, loss of F and H waves consistent with peripheral demyelination. Metabolic screening should be included as a part of initial work-up by including blood lactate, ammonia, blood and urine amino acids, urine organic acids analysis, if available (aminoacidopathies, urea cycle defects, and mitochondrial disorders). Other assays may include carnitine levels, plasma acylcarnitine profile may be helpful to identify fatty acid oxidation disorders. Specialized scans (MIBG), other body scans may be considered when paraneoplastic disorders are in the differential. The approach is summarized in **Figure 1**.

INTERMITTENT/EPISODIC ATAXIA

Episodic Ataxia 1

Episodic ataxia 1 (EA1) is a rare autosomal-dominant disorder and represents a channelopathy. It is caused by point missense mutations that affect the human voltage-gated potassium channel (*KCNA1* gene on band 12p13). Affected individuals report continuous myokymia between attacks of ataxia that last for seconds to minutes. Ataxia of an episodic nature may also be accompanied by focal epileptic seizures (some individuals in affected families). Symptoms are precipitated by movement, startle, or emotion. Electroencephalography (EEG) may show continuous rhythmic muscle discharge artifact, which may become more prominent with hyperventilation. Electromyography is the only helpful investigation; it usually demonstrates continuous motor unit activity in all patients. Partial responses to acetazolamide, carbamazepine, phenytoin, and phenobarbital have been reported.

Episodic Ataxia 2

Episodic ataxia 2 (EA2) is an autosomal-dominant disorder that has been associated with mutations that affect the calcium channel (*CACNA1A*) gene at the 19p13 locus. It is allelic to familial hemiplegic migraine and spinocerebellar ataxia type 6 (SCA6), wherein mutations affecting the same gene have been described. Intermittent midline cerebellar dysfunction characterized by bouts of ataxia, nystagmus, dysarthria, and vertigo occurs. Headache can be a feature in some families and the absence of myokymia is notable. Attacks are triggered by stress, exercise, and fatigue, among others. The diagnosis is confirmed by *CACNA1A* gene mutation testing. A few patients with EA2 may respond to acetazolamide.

CHRONIC ATAXIA

The discussion below addresses selected conditions that are associated with chronic ataxia within the framework of the classification schema adopted in this chapter.
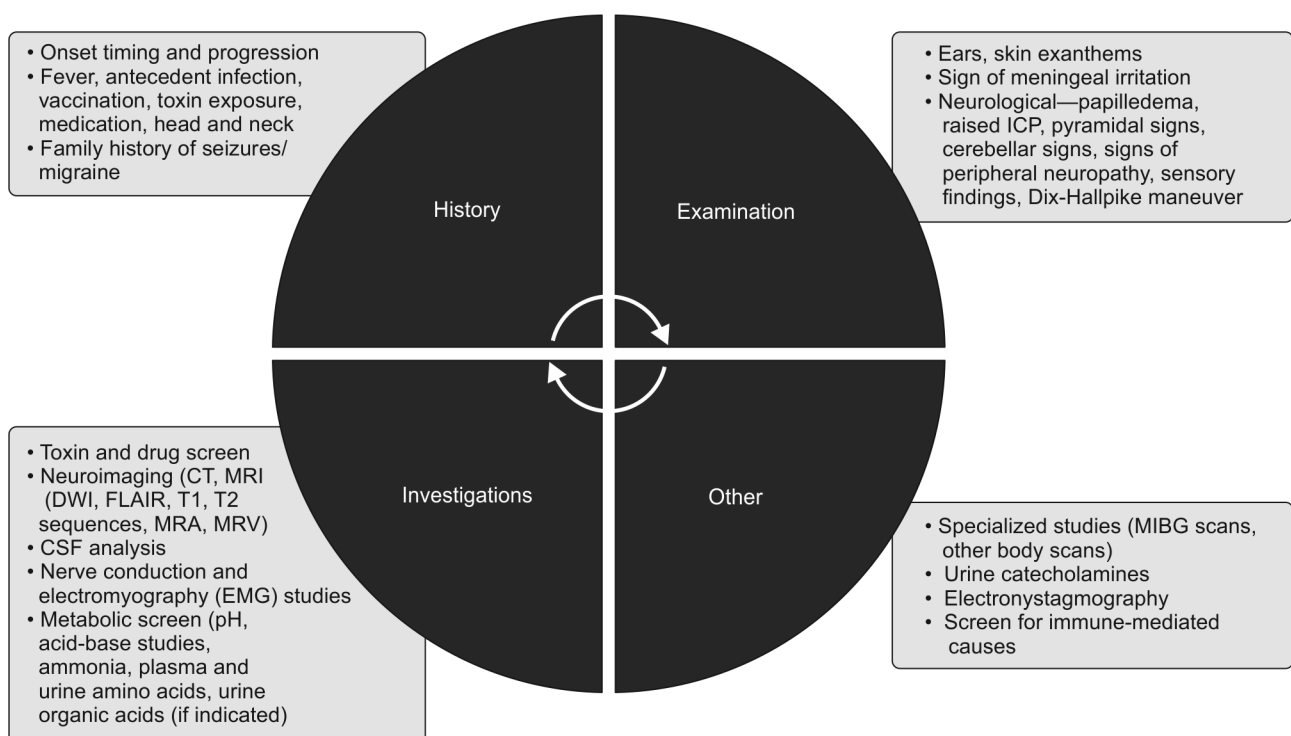
Figure 1 Investigations for acute childhood ataxia

Nonprogressive Cerebellar Ataxias (NPCA)

Early features in the first few years of life include; hypotonia, developmental delay, feeding difficulties and oromotor apraxia, speech delay secondary to articulatory difficulties, ataxia and cognitive difficulties may be recognized at a later age. Genetic assessments of the family may disclose a specific pattern of inheritance.

Laboratory findings Genetic mutation tests available only in selected conditions, for example, for Joubert syndrome. Metabolic screening is usually negative. MRI is superior as it permits better visualization of the posterior fossa. Variable degrees of hypoplasia of cerebellar vermis are usually reported. In severe cases, the entire vermis may be absent, and associated abnormalities in cerebellar hemispheres noted. In mild cases, however, the cerebellum is morphologically normal on imaging studies. Associated abnormalities of the brainstem and supratentorial structures may be of additional value in the diagnosis of syndromes such as Dandy-Walker malformation.

Joubert Syndrome

Currently, a group of conditions termed Joubert syndrome and related disorders (JSRDs), share the neuroimaging finding of *molar-tooth* sign as a common feature. The neurological presentation of JS includes hypotonia evolving into ataxia, developmental delay, abnormal eye movements, and neonatal breathing abnormalities. Multiorgan involvement, mainly of the retina, kidneys, and liver, is of a variable nature. To date, 16 causative genes have been identified, encoding for proteins expressed in the primary cilium or its apparatus leading to the description of a growing field of disorders due to mutations in ciliary proteins that are collectively known as *ciliopathies*. These include isolated nephronophthisis, Senior-Loken syndrome, Bardet-Biedl syndrome and, in particular, Meckel syndrome, which is allelic at JSRD at seven distinct loci. Significant genotype-phenotype correlates are emerging between specific clinical presentations and mutations in JSRD genes, with relevant implications in terms of molecular diagnosis and clinical follow-up.

PROGRESSIVE RECESSIVELY INHERITED ATAXIAS

Friedreich Ataxia

Friedreich ataxia was the first identified recessively inherited condition with a mutation involving a triplet repeat expansion. Ninety-six percent of patients are homozygous for a GAA expansion in intron 1 of the *X25* gene. The number of GAA repeats ranges from 7 to 38 in normal alleles and from 66 to greater than 1700 triplets in disease-causing alleles. The remaining cases are compound heterozygotes for a GAA expansion and a frataxin point mutation. The mutation leads to formation of the abnormal protein termed *frataxin*. The cells and tissues carrying this mutation appear to be sensitive to oxidative stress.

Clinical Features

A variable age of onset is noted, the key neurological features include; cerebellar ataxia, dysarthria, nystagmus, uncoordinated limb movements, hypoactive knee and ankle deep tendon reflexes, Babinski sign, impaired position sense, and impaired vibratory sense. Systemic involvement includes cardiac and skeletal features; symmetric, concentric, hypertrophic cardiomyopathy associated subaortic stenosis, eventually leading to congestive heart failure, while the skeletal features include; pes cavus, scoliosis, and hammer toes. An abnormal glucose tolerance test, diabetes mellitus, and diabetic ketoacidosis are late manifestations.

Laboratory Findings

An electrocardiogram, and echocardiogram are part of the cardiac assessment. Nerve conduction and EMG will confirm the involvement peripheral nerves. Imaging studies of the nervous system disclose cerebellar atrophy and a thin spinal cord. Research studies confirm impaired oxidative evidence of iron accumulation within mitochondria of FRDA fibroblasts subjected to oxidative stress, resulting in impaired respiratory function. Molecular genetic testing is available.

Treatment

No specific treatment other than symptomatic and supportive care is available. Treatment protocols currently involve the use of Coenzyme Q and other antioxidants that are being newly developed (mitoquinone, idebenone). Preliminary trials suggest clinical improvements based on the bioenergetics of cardiac and skeletal muscle, and slowing of progression.

Ataxia with Selective Vitamin E Deficiency

This is a rare autosomal-recessive disorder resulting from a mutation that affects the gene for alpha-tocopherol transfer protein. It is phenotypically similar to Friedreich ataxia, with head titubation (28%), spinocerebellar ataxia, areflexia, and proprioception loss. Skin is affected by xanthelasmata and tendon xanthomas. Age of onset varies between 2 years and 52 years and usually occurs when younger than 20 years and slowly progresses over decades. Low-to-absent serum vitamin E and high serum cholesterol, triglyceride and beta-lipoprotein are characteristic of this disorder. Treatment consists of vitamin E supplementation. A dose of 400–1200 IU/day improves neurologic function. This should be maintained for life.

Coenzyme Q (10) (CoQ)/Ubiquinone Deficiency

This is an autosomal recessive disorder presenting with five phenotypes: a myopathic form, a severe infantile neurological syndrome associated with nephritic syndrome, an ataxic variant, Leigh syndrome and a pure myopathic form. CoQ (10) or ubiquinone plays a key role in oxidative phosphorylation (OXPHOS) in that it distributes electrons between the various dehydrogenases and the cytochrome segments of the respiratory chain. Cerebellar ataxia is the most common phenotype. Muscle CoQ deficiency associated with cerebellar ataxia and cerebellar atrophy as the main neurological signs. Biochemically, the hallmark of CoQ deficiency syndrome is a decreased CoQ concentration in muscle and/or fibroblasts. Patients with primary CoQ deficiency may benefit from CoQ supplementation, although the clinical response varies even among patients with similar phenotypes.

Abetalipoproteinemia

This rare autosomal-recessive disorder is characterized by low levels of low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs) in the blood. The biochemical basis is attributable to defective assembly and secretion of apolipoprotein B (Apo-B)–containing lipoproteins by the intestines and the liver as mutations appear to affect the microsomal triglyceride transfer protein (*MTP*) gene.

Clinical Features

The early features are of abnormalities of tone, areflexia, proprioceptive dysfunction, loss of reflexes, and Babinski sign (prominent findings). By 5–10 years, gait disturbances and cerebellar signs appear. Associated gastrointestinal manifestations in the early years include; a malabsorptive steatorrhea and abdominal distension. Pes cavus and scoliosis present in some patients, while pigmentary retinopathy leads to visual symptoms at a late stage.

Laboratory Findings

Acanthocytosis on peripheral blood smears is a constant finding, the lipid profile shows decreased levels of serum cholesterol, elevated high-density lipoprotein cholesterol, low LDL and VLDL and triglyceride levels. Molecular genetic testing is available.

Treatment

High-dose supplementation of vitamin E has a beneficial effect on neurologic symptoms and other fat-soluble vitamins (D, A, K) must be supplemented to correct secondary deficiency related to the malabsorptive state.

Hypobetalipoproteinemia

The condition is clinically indistinguishable from abetalipo-proteinemia especially in its homozygous form, but the inheritance is autosomal dominant. It is caused by mutations that affect the *Apo-B* gene, which affects turnover of apolipoprotein B. Laboratory findings are characterized by extremely low plasma levels of apolipoprotein B, as well as low levels of total- and low-density lipoprotein (LDL) cholesterol values.

Ataxia Telangiectasia

This progressive, recessively inherited ataxia presents in early childhood. A defective truncated protein that belongs to the (possibly phosphatidylinositol-3 kinase family of proteins) results from mutations that affect the *ATM* gene locus. The function of this protein is to phosphorylate key substrates that are involved in DNA repair. The disease begins when patients are aged 1–3 years.

Clinical Features

Extrapyramidal features include; gait abnormalities, choreo-athetosis, dystonia, and oculomotor apraxia in the early stages. Progressive ataxia and slurred speech and features of a cerebellar syndrome also become evident. Immunodeficiency and increased susceptibility to infections is common, cutaneous and bulbar telangiectasia (present in teenagers and older individuals) appear later and are of clinical diagnostic value. Due to abnormal chromosomal fragility and DNA repair defects, there is an increased susceptibility to cancer (e.g., leukemia, lymphoma).

Laboratory Findings

Molecular genetic testing is performed for mutations affecting the *ATM* gene locus (11q22.3). For those patients in whom mutations cannot be identified, other supportive laboratory evidence must be sought. Elevated (>10 ng/mL) serum alpha-fetoprotein in 90–95% of patients is often supportive evidence in the face of clinical features and can be a useful marker. Abnormalities in colony survival assay (colony formation of a lymphoblastoid cell line following irradiation) as well as karyotyping abnormalities involving 7–14 chromosomal translocation in 5–15% of cells after phytohemagglutinin stimulation of lymphocytes in peripheral blood may demonstrate breakpoints involved in translocation at the 14q11 and 14q32 sites.

Ataxia Telengiectasia Like Disorders

This group includes the following disorders; ataxia with oculomotor apraxia type 1 (AOA1), ataxia with oculomotor apraxia type 2 (AOA2) and ARSACS.

Ataxia with Oculomotor Apraxia Type I (AOA1)

The disorder begins in childhood with an onset between 2 years and 10 years proceeding to loss of ambulation in 7–10 years. The gene (*APTX*) locus at 9p13.3 codes for a protein aprataxin which appears to have a role in DNA repair. Initially, the disorder presents as a cerebellar ataxia, followed in a few years by oculomotor apraxia

progressing to complete ophthalmoplegia are key features. Chorea and upper limb dystonia are common. While normal cognition is reported in Portuguese families, decline in cognition is noted in Japanese kindred. Areflexia associated with motor neuropathy is an added feature in more than 90% cases. Neuroimaging shows marked cerebellar atrophy in affected individuals, and the EMG will demonstrate signs of axonal neuropathy.

Ataxia with Oculomotor Apraxia Type 2 (AOA2)

The disorder begins in the second decade (3–30 years) with slow progression. Mutations are described in the *SETX* gene, located at 9q34 and the gene product is called *senetaxin*, the protein is thought to function as a helicase involved in RNA maturation and termination. Similar to *AOA1*, progressive cerebellar ataxia and oculomotor apraxia are key features. Areflexia associated with an axonal sensorimotor neuropathy leads to loss of ambulation. Pyramidal signs and dystonia are added features. Affected patients uniformly demonstrate cerebellar atrophy on MR imaging while elevated alphafetoprotein (> 20 ng/mL) but generally lower than seen in ataxia-telengiectasia. Elevated serum cholesterol is seen in almost 50% of affected individuals. Supportive and rehabilitative measures are the only options currently available.

Infantile-onset Spinocerebellar Ataxia

Infantile-onset spinocerebellar ataxia (IOSCA) is an autosomal recessive neurodegenerative condition characterized by signs of developmental regression usually after the first year, followed by appearance of ataxia, generalized hypotonia, loss of deep-tendon reflexes, and athetosis. By the age of seven years, ophthalmoplegia and sensorineural deafness are evident. In later years, there is loss of ambulatory capacity; sensory axonal neuropathy, optic atrophy, autonomic nervous system dysfunction, and hypergonadotrophic hypogonadism in females become evident. Myoclonic jerks or focal clonic seizures that progress to epilepsia partialis continua followed by status epilepticus and an epileptic encephalopathy represent a catastrophic phenotype. Mutations in *C10orf2* gene form the basis of this disorder, which leads to a form of mitochondrial DNA depletion particularly in the nervous system. Both homozygous and compound heterozygous mutations are described.

Management

All routine screening and metabolic tests are normal, muscle pathology is normal, the liver may show mitochondrial DNA depletion. Targeted mutational analysis is available. No definitive treatment is available. Valproic acid should be avoided in treatment of epilepsy.

PROGRESSIVE DOMINANTLY INHERITED ATAXIAS

Spinocerebellar Ataxias

The number of dominantly inherited spinocerebellar ataxias (SCA) that have been described has increased to 26 and are labeled SCA1 onwards in sequence. The genetic basis for most of these disorders is related to expansion of triplet nucleotide repeats. A great degree of overlap in phenotype is noted including the age of onset, with the major group of symptoms related to cerebellar and spinocerebellar pathway dysfunction. Neuroimaging studies are relatively non-specific findings. These mostly affect adults, rarely children may be affected. The majority of the SCA are accounted for by SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8 subtypes, the remaining types are quite rare and have been reported in few families from both Caucasian and non-Caucasian background. SCA1, 2 and 3 have been reported in the South Indian population and account for more than a third of cases. SCA12 seems to be prevalent in the

Indian context Agarwal ethnic background. Spinocerebellar ataxia (SCA-2) and SCA-8 may rarely present in children. Clinical features of SCA2 include the following; age of onset (2–65) years. Ataxia, facial fasciculation, lid retraction, reduced ocular saccadic velocity are key features. The gene locus is 12q24.1 and the SCA 2 protein product is termed ataxin 2. The CAG repeat expansion in affected individuals is 34–400 (15–31 normal range). Spinocerebellar ataxia (SCA-8) is linked to an untranslated CTG expansion on 13q21. Clinical features include onset of symptoms ranging from age 18–65 years, with a mean of 39 years. Dysarthria and gait instability (commonly initial symptoms) examination findings include spastic dysarthria, nystagmus, limb spasticity, limb and gait ataxia, and diminished vibration perception. Progression is generally slow.

APPROACH TO A PATIENT WITH A SUSPECTED INHERITED ATAXIA

The assessment of the patient involves obtaining a detailed clinical history complemented by an appropriate neurological examination that delineates the following information:

- Age of onset
- Mode of onset (acute, subacute, chronic)
- Sex
- Natural history (nonprogressive/static, episodic, or progressive)
- Associated symptoms/signs that provide localizing information:
    – Presence of dystonia, chorea suggesting involvement of the striatum
    – Proprioceptive dysfunction suggesting involvement of spinocerebellar pathways
    – Visual deficits (retinitis pigmentosa), auditory involvement (Refsum disease)
    – Cognitive dysfunction may be encountered early and or late
    – Fluctuation of symptoms, triggers such as exercise, etc.
- Other systemic features
    – Dysmorphic features and associated congenital malformation that may suggest a specific association or clinical syndrome.
    – Cardiac (Friedreich ataxia), renal (NPCA), cutaneous (Xeroderma pigmentosa) are examples
- Family history and pedigree analysis will provide diagnostic clue and information on possible patterns of inheritance, useful for planning investigations and genetic counseling.

Once a specific clinical phenotype is delineated, the investigative process can be initiated based on the clinical features. The initial step involves obtaining an MRI. Genetic studies should include; karyotype, array CGH (deletions, duplications and chromosomal rearrangements) and specialized cytogenetic studies (Angelman syndrome), and DNA-based molecular diagnostics (spinocerebellar ataxias, recessively inherited ataxias (AOA1, AOA2, IOSCA, Ataxias associated with DNA repair defects) can be utilized to provide rapid turnaround times for diagnosis. These tests are offered through many molecular genetic laboratories around the world. Disease specific information is available at *http://www.genetests.org.*

Biochemical studies should include; acid-base studies, blood lactate and ammonia levels, Vitamin E levels, serum alpha-fetoprotein, cholesterol, lipid profiles, lipoprotein electrophoresis should be included. CSF studies should include glucose, lactate and a simultaneous blood sugar assay in addition to routine studies. Metabolic screening would involve tests such as quantitative studies for serum carnitine levels, amino acids in blood and urine, urine analysis for organic acid and acylglycines (Gas Chromatography-Mass Spectrometry (GC/MS)), plasma acylcarnitines (tandem mass spectrometry MS/MS), assays for sialotransferrins (isolectric focusing of serum transferrins) should be used selectively. Invasive tests such as nerve conduction and electromyography can be useful in exploring sensory and motor components of peripheral nerve involvement. Muscle biopsy studies include; histopathology, CoQ assays, respiratory chain studies on fresh muscle may be indicated in the context of CoQ deficiency and respiratory chain defects, mtDNA depletion (low mtDNA/nDNA ratio in tissues). An algorithmic approach is suggested **(Flow chart 1)**. Molecular diagnostic confirmation can follow targeted mutation analysis for pathogenic mutations in known genes. If molecular genetic tests are negative, third generation sequencing technologies (whole exome or whole genome sequencing) can be resorted to.

MORE ON THIS TOPIC

De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: current state of the art. Seizure. 2013;22:803-11.

Fogel BL. Childhood cerebellar ataxia. J Child Neurol. 2012;27:1138-45.

Musselman KE, Stoyanov CT, Marasigan R, et al. Prevalence of ataxia in children: a systematic review. Neurology. 2014;82:80-9.

Nemeth AH, Kwasniewska AC, Lise S, et al. Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. Brain. 2013;136:3106-18.

Pandolfo M. Friedreich ataxia. Semin Ped Neurol. 2003;10:163-72.

Parker CC, Evans OB. Metabolic disorders causing childhood ataxia. Semin Ped Neurol. 2003;10:193-9.

Salman MS, Lee EJ, Tjahjadi A, Chodirker BN. The epidemiology of intermittent and chronic ataxia in children in Manitoba, Canada. Dev Med Child Neurol. 2013;55:341-7.

Sinha KK, Worth PF, Jha DK, et al. Autosomal dominant cerebellar ataxia: SCA2 is the most frequent mutation in eastern India. J Neurol Neurosurg Psychiatry. 2004;75:448-52.

van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol. 2006;5:413-23.

Vedolin L, Gonzalez G, Souza CF, et al. Inherited cerebellar ataxia in childhood: a pattern-recognition approach using brain MRI. AJNR. 2013;34:925-34. .

Whelan HT, Verma S, Guo Y, et al. Evaluation of the child with acute ataxia: a systematic review. Pediatr Neurol. 2013;49:15-24.

IN A NUTSHELL

1. Ataxia is defined as an inability to maintain normal posture and smoothness of movement.
2. The etiology of acute ataxia is diverse and includes parainfectious, toxic-metabolic, vascular/ischemia, immune-mediated inflammation, trauma, tumors, and paraneoplastic conditions.
3. Chronic pediatric ataxias have structural, genetic and metabolic causes.
4. Episodic ataxias are rare autosomal-dominant disorders.
5. Joubert syndrome and related disorders (JSRDs), share the neuroimaging finding of "molar-tooth" sign as a common feature.
6. Friedreich ataxia is characterized by cerebellar ataxia, dysarthria, nystagmus, uncoordinated limb movements, hypoactive knee and ankle deep tendon reflexes, Babinski sign, impaired position sense, impaired vibratory sense; and cardiac and skeletal involvement.
7. Abetalipoproteinemia is characterized by acanthocytosis decreased levels of serum cholesterol, elevated high-density lipoprotein cholesterol, low LDL and VLDL and triglyceride levels.
8. Ataxia telangiectasia results from mutations that affect the *ATM* gene locus.
9. Infantile-onset spinocerebellar ataxia (IOSCA) is an autosomal recessive neurodegenerative condition characterized by signs of developmental regression usually after the first year, followed by appearance of ataxia, generalized hypotonia, loss of deep-tendon reflexes, and athetosis.
10. Spinocerebellar ataxias are dominantly inherited and numbered as SCA1 to SCA26.

Flow chart 1 Approach to chronic ataxia

Approach to chronic ataxia
Clinical presentation
1. Age of onset
2. Symptoms (Episodic, progressive ataxia plus other neurologic features)
3. Progression
4. Family history—consanguinity, three generation pedigree

Neuroimaging studies
CT, MRI head, MRS can be helpful in identifying cerebellar atrophy, hypoplasia,
specific features such as the molar tooth sign, white matter and gray matter involvement

| Acute episodic/ intermittent ataxia | Progressive ataxia with spinocerebellar dysfunction | *Progressive ataxia* plus includes disorders that have complex neurological features +/–multisystem involvement | Ataxia plus myoclonic epilepsies |

Episodia ataxia (EA1, EA2)
• MSUD
• Hartnup disease
• Fatty acid
• Oxidation defects
• Late onset urea cycle defects

Dominant:
• Spinocerebellar ataxias (SCA)
• Recessive ataxias
• Friedreich's ataxia
• Vitamin E associated ataxia
• Abetalipoproteinemia
• Refsum's disease

Ataxia telangiectasia:
• AOA1 and AOA2
• IOSCA
• Disorders of glycosylation syndromic—Angelman's syndrome

Lafora body:
• Neuronal ceroid
• Lipofuscinosis
• MERRF
• POLG

Molecular genetic testing:
• Appropriate gene testing selection
• Metabolic screening, where indicated

Molecular genetic testing:
• SCA panel
• Friedreich's ataxia
• Metabolic tests where indicated*
• Vitamin E deficiency

Molecular genetic testing:
• Skin and muscle biopsy
• EM studies on skin
• Respiratory chain studies
• Mt DNA depletion studies

*Metabolic screening tests**
• Smears for acanthocytes, vacuolated lymphocytes
• Acid-base studies
• Blood gases
• Serum uric acid
• Plasma ammonia
• Plasma lactate
• Vitamin E levels
• Serum alfa-fetoproteins
• Phytanic acid levels
• Amino acid screening in plasma, urine and CSF
• Urine organic acid profile
• Biotinidase levels
• Liver function tests
• Plasma cholesterol, triglycerides, lipoprotein electrophoresis
• CT and MRI brain and spinal cord
• Nerve conduction EMG studies
• Evoked potentials, auditory and somatosensory EEG
* These tests are not necessary in every patient, but more targeted screening based on presentation is recommended

Specific testing:
• Chromosomal studies, array CGH
• Methylation studies, UB3E mutation analysis
• Isoelectric focusing of sialotransferrins
• Mitochondrial DNA mutation studies
• Specific enzyme assays on serum, leukocytes and cultured fibroblasts
• Trageted mutation analysis
• Depending on condition
• Whole exome sequencing*
• Whole genome sequencing*
• Whole exome and whole genome sequencing are 3rd generation sequencing platforms

* Whole exome sequencing and whole genome sequencing are 3rd generation sequencing platforms

Chapter 42.25
Neurometabolic Disorders
Mahesh Kamate

Inborn errors of metabolism (IEM) are genetically transmitted disorders that result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins across cell membrane or mitochondria. As a result of this defect, there is accumulation of substances, deficiency of critical intermediary or final products and noxious excess of products of alternative metabolic pathways causing various symptoms and signs. Brain being one of the most metabolically active organs of the body, gets affected in many IEM resulting in various neurological manifestations. Hence, many of the IEMs also qualify for the term *neurometabolic disorders*. The neurometabolic disorders that have a relentlessly progressive course with irreversible loss of function are termed as *neurodegenerative disorders*.

Correct diagnosis is vital for institution of specific therapy, counseling of parents, to know the natural history of the disease, and for prenatal diagnosis. There are many misconceptions with regards to IEM like they happen only in those with a positive family history, they are difficult to diagnose and confirm, and biochemical pathways are impossible to remember. But the work-up should progress from broad widely available tests to specific ones and complex pathways are not the important part of the evaluation.

CLINICAL PRESENTATIONS

Six common neurologic presentations are described in IEM.
1. *Chronic encephalopathy:* With or without non-neural involvement
2. Acute encephalopathy
3. Stroke
4. Movement disorder
5. Myopathy with or without myoglobinuria
6. Psychiatric or behavioral abnormalities like extreme hyperactivity, agitation, psychoses, anxiety/depression.

1. Chronic Encephalopathy

Here presentation could be in the form of gray matter disease (poliodystrophy) manifesting as psychomotor retardation or dementia, seizures, impairment of special senses, and extra-pyramidal disturbances or white matter disease (leukodystrophy) presenting as motor difficulties, disorders of tone, ataxia and optic atrophy with or without peripheral neuropathy. The disorders with chronic encephalopathy can again be classified as those with and without non-neural involvement like hepatosplenomegaly, muscle involvement, skeletal involvement, skin and connective tissue involvement. The details are given in the next chapter on neurodegenerative disorders.

Psychomotor retardation/dementia is one of the most common neurological presentations of chronic encephalopathy secondary to IEM. It is usually global but the children are better in verbal skills versus motor skills. There is severe irritability, impulsivity, aggressiveness and hyperactivity. Nocturnal restlessness is very characteristic and there is progressive deterioration and associated with other features like tone abnormalities, special senses, seizures, pyramidal signs, cranial nerves, peripheral nerve involvement.

Seizures in IEM as a part of chronic encephalopathy are usually recurrent without obvious cause like hypoglycemia, have onset early in life, are associated with other neurological signs. They are usually complex partial or myoclonic seizures and are resistant to conventional antiepileptic drugs.

2. Acute Encephalopathy

The earliest signs of encephalopathy may be no more obvious than excessive drowsiness, unusual behavior, or some unsteadiness of gait. Acute or intermittent ataxia is a common sign of acute encephalopathy in older children with inborn errors of metabolism. A history of recurrent attacks of unsteadiness of gait or ataxia, especially when associated with vomiting or deterioration of consciousness, should be considered a strong indication for investigation of a possible inherited metabolic disease. It can rapidly progress to coma in a few cases in the absence of prompt treatment. Absence of focal neurological deficits and fluctuation in the clinical severity of encephalopathy are particulars pointers to IEM in a given child with acute encephalopathy. Many disorders of intermediary metabolism and disorders of energetic processes (mitochondrial and cytoplasmic) present as acute encephalopathy.

3. Stroke or Acute Onset Focal Neurological Deficits

An increasing number of inborn errors of metabolism have been reported to be associated with stroke or stroke like episodes. The important ones are listed in **Box 1**.

4. Movement Disorders

Extrapyramidal movement disorders in patients with inborn errors of metabolism are almost always associated with neurologic signs referable to other parts of the nervous system. They can be in the form of choreoathetosis, dystonia, tremors, rigidity, ataxia or myoclonus. It is typically seen in disorders such as organic acidemia and urea cycle defects. Seizures or epilepsy as a presentation is discussed in the next section in this chapter.

5. Myoglobinuria

Many of the disorders of glycolysis and fatty acid oxidation present with exercise intolerance and cramps with myoglobinuria. The disorders of glycolysis are characterized by severe muscle cramps shortly after the initiation of intense exercise. Mild, sustained exercise, such as level walking, usually is well-tolerated. Typically, if the patient rests briefly, moderate levels of activity can be resumed without discomfort. This is the so-called *second-wind* phenomenon. The painful episodes of cramps are often followed within hours by the development of wine-colored pigmentation of the urine (myoglobinuria) as a result of rhabdomyolysis. Creatine phosphokinase (CPK) levels are typically markedly elevated and rise further during exercise. Sometimes it is severe enough to cause acute renal failure. The disorders of glycolysis presenting as myoglobinuria include McArdle disease (myophosphorylase deficiency), muscle phosphofructokinase (PFK) deficiency (GSD VII), phosphoglycerate kinase deficiency, phosphoglycerate mutase and lactate dehydrogenase.

In patients with myopathy resulting from defects in fatty acid oxidation, the muscle cramps and tenderness characteristically develop after periods of exercise, when the patient is actually

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> **BOX 1** Inborn errors of metabolism associated with stroke or stroke like episodes
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> 1. Homocystinuria, including MTHFR deficiency and cobalamin defects
> 2. Fabry disease
> 3. Methylmalonic acidemia
> 4. Propionic acidemia
> 5. Isovaleric acidemia
> 6. Glutaric aciduria, types I and II
> 7. Ornithine transcarbamylase (OTC) deficiency
> 8. MELAS
> 9. CDG type Ia (carbohydrate-deficient glycoprotein syndrome, type Ia)

at rest, and the muscle is drawing heavily on fatty acid oxidation to meet its energy requirements. There is history of episodic muscle stiffness, pain, tenderness, weakness, and myoglobinuria precipitated by prolonged exercise, exposure to cold, fasting, or intercurrent infection. Here the patients do not experience a 'second-wind' phenomenon. Between attacks, they may be completely asymptomatic, though some experience residual muscle weakness and fatigability. The CPK is elevated during attacks, but it is generally normal at other times. The fatty acid oxidation disorders presenting with myoglobulinuria include carnitine-palmitoyl transferase II deficiency, long chain acyl CoA dehydrogenase deficiency, short chain acyl CoA dehydrogenase deficiency and myoadenylate deaminase deficiency.

6. Psychiatric-behavioral Manifestations

Some neurometabolic disorders are characterized by severe behavior problems. Children with mucopolysaccharidoses have severe hyperactivity, impulsiveness, short attention span, poor tolerance of frustration, aggressiveness, and sleeplessness. Infants with hepatorenal tyrosinemia commonly exhibit acute episodes of extreme irritability. Personality changes are a common feature of Wilson disease, but usually only after the development of other neurologic manifestations of the disease. Few of the urea cycle disorders like hyperammonemia-hyperornithinemia-homocitrullinemia (HHH) syndrome have experienced periodic episodes of acute hallucinatory states lasting up to a few hours. The episodes generally occurred during periods of hyperammonemia, and the frequency of attacks decreased with improved metabolic control. Porphyria can present as chronic anxiety and depression, and marked restlessness, insomnia, depression, paranoia, and sometimes, hallucinations (during acute crises). Lesch-Nyhan syndrome presents with severe self-mutilatory behavior while presentation as acute schizophrenia has been reported with homocystinuria. Chronic forms of neurometabolic disorders like adrenoleukodystrophy can present with severe attention deficit hyperactivity and poor school performance before the onset of spasticity and visual impairment. Late onset forms of metachromatic leukodystrophy can present with social withdrawal, irritability, schizophrenia and mood disorders. Late onset GM2 gangliosidosis presents with acute psychosis, obsessional paranoia and hallucinations.

INBORN ERROR OF METABOLISM (IEM) PRESENTING AS SEIZURES AND EPILEPSY

Seizures are a common symptom in a great number of metabolic disorders, occurring mainly in infancy and childhood. In few disorders, it is the only or the predominant manifestation and hence it is important to consider neurometabolic disorder whenever we have a child presenting with seizures/epilepsy especially when it is not responding to treatment as expected. It is very important to note that few of these respond to vitamins/cofactors and have a good outcome if diagnosed earlier. Neurometabolic conditions presenting with neonatal seizures are listed in **Box 2**; and those presenting in later childhood are enumerated in **Box 3**.

Clues for IEMs as a Cause of Seizures

A positive family history of similar seizures may be seen as most of these are autosomal recessive conditions. A few of them can present as in utero hiccups and some can cause seizures in utero. Myoclonic type of seizures when present also may point to a possibility of metabolic disorders. Most of them are usually associated with encephalopathy and they may be depressed at birth. IEMs should always be considered even if there is a positive history of hypoxic ischemic encephalopathy. Presence of dysmorphic features could point to mitochondrial disorders or

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BOX 2 IEMs presenting with seizures in neonatal period

1. Vitamin dependent seizures
   a. Pyridoxine dependency
   b. Pyridoxal phosphate dependency
   c. Folinic acid responsive seizures
2. Amino acid disorders, including neurotransmitter abnormalities
   a. GABA transaminase deficiency
   b. Nonketotic hyperglycinemia (glycine encephalopathy)
   c. Sulfite oxidase deficiency & molybdenum cofactor deficiency
3. Metal disorders like Menke's disease
4. Urea cycle disorders
5. Organic acidurias
6. Aminoacidurias
7. Mitochondrial disorders
8. Peroxisomal disorders

BOX 3 IEMs presenting as seizures in infancy, childhood and adolescence

1. Biotinidase deficiency
2. Methylmalonic acidemia
3. Hyperhomocysteinemia
4. Pyridoxine dependency (Children less than 3 years)
5. Glut-1 deficiency syndrome
6. Serine synthesis disorders
7. Creatine synthesis disorders
8. Purine metabolic defects
9. GABA transaminase deficiency
10. Carbohydrate deficiency glycoprotein disorders
11. Some of the progressive myoclonic epilepsies
    a. Myoclonic-epilepsy with ragged red fibers (MERRF)
    b. Ceroid lipofuscinoses
    c. Sialidoses

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peroxisomal disorders. Burst-suppression pattern on EEG should also make one consider IEM in a given case. In older children presence of associated global developmental delay, involuntary movements, pigmentary changes, lens dislocation, abnormal body odor, skin and hair changes and organomegaly are important pointers to neurometabolic disorders.

Seizure Types

Table 1 correlates the typology of seizure with etiology of neurometabolic disorder. The neurometabolic disorders can present as various syndromic phenotypes with different seizure types such as early myoclonic encephalopathy, early infantile epileptic encephalopathy, infantile spasms, and myoclonic epilepsies. They have various degrees of treatability at present, with some requiring prompt diagnosis and intervention to avoid otherwise catastrophic outcomes. The common treatable disorders are mentioned in **Table 2**.

Glucose Transporter-1 (GLUT-1) Deficiency

Glucose transporter type I facilitates the passage of glucose across the blood-brain barrier, and its dysfunction in the developing brain leads to the development of a metabolic encephalopathy. CSF shows hypoglycorrhachia associated with normal plasma glucose and low-to-normal CSF lactate (CSF to blood glucose ration of less than 0.45), measured in a fasting state. A wide array of phenotypes has been associated with this disorder, but 90% of affected children develop epilepsy (of various types, including absence, focal, generalized myoclonic, clonic, tonic, and nonconvulsive status epilepticus). Microcephaly, ataxia, and psychomotor delay may be present, but patients may also suffer from epilepsy without any accompanying motor or cognitive deficiencies. EEG findings vary and may be normal, but usually include either focal or generalized

Table 1 Seizure types in neurometabolic disorders

Seizure type	Neurometabolic disorder
Infantile spasms	Biotinidase deficiency, Menkes disease, mitochondrial disorders, organic acidurias, amino acidopathies
Myoclonic seizures	Nonketotic hyperglycinemia, mitochondrial disorders, GLUT-1 deficiency, storage disorders, MERRF
Progressive myoclonic epilepsies	Lafora disease, mitochondrial disorders like MELAS and MERRF, Unverricht-Lundborg disease, sialidosis
Epilepsy with generalized tonic-clonic seizures	GLUT-1 deficiency, neuronal ceroid lipofuscinosis, other storage disorders, mitochondrial disorders
Epilepsy with myoclonic-astatic seizures	GLUT-1 deficiency, neuronal ceroid lipofuscinosis
Epilepsy with (multi-)focal seizures	Neuronal ceroid lipofuscinosis 3, GLUT-1 deficiency and others
Epilepsia partialis continua	Alpers disease, other mitochondrial disorders

Abbreviations: MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers.

Table 2 Treatable neurometabolic disorders presenting as epilepsy

Condition	Therapy
GLUT-1 deficiency	Ketogenic diet
Cofactor-dependent epilepsy	Pyridoxine, pyridoxal phosphate, folinic acid, biotin
GAMT deficiency	Creatine supplementation, arginine-restricted, ornithine-enriched diet
Phenylketonuria	Low-phenylalanine diet; in atypical phenylketonuria substitution of L-DOPA, 5OH-tryptophan, folinic acid
Defects of serine biosynthesis	Serine supplementation
Disorders of CoQ biosynthesis	Coenzyme Q supplementation
Autosomal recessive methylene tetrahydrofolate reductase deficiency	Betaine and methionine supplementation

Abbreviation: GAMT, guanidinoacetate methyltransferase.

slowing or attenuation, or spike-and-wave discharges (generalized, focal, or multifocal). Neuroimaging results may demonstrate diffuse atrophy.

Glucose transporter I deficiency has emerged as the leading metabolic indication for the ketogenic diet, a dietary therapy that replaces glucose with ketone bodies as the primary biochemical energy source. Response is rapid, even in the case of formerly refractory seizures, and treatment should be maintained long-term. Additionally, there are certain compounds known to inhibit Glut-1, including phenobarbital, diazepam, methylxanthines (theophylline, caffeine), and alcohol, which should be avoided.

Pyridoxine, Folinic Acid, and Pyridoxal-5-Phosphate-dependent Epilepsies

There are various epileptic encephalopathies related to vitamin B_6 metabolism, and pyridoxine-dependent epilepsy (PDE) is the prototype, resulting from a loss of the biologically active pyridoxal-5-phosphate (PLP) due to a dysfunction of the protein antiquitin (ALDH7A1). PDE normally presents within the first hours following

birth with serial refractory seizures responsive to pyridoxine administration. Trials of systemic pyridoxine administration require close cardiorespiratory monitoring. Diagnosis is based on demonstrating increased levels of pipecolic acid and alpha-aminoadipic semialdehyde (AASA) in blood and CSF and genetic studies for *ALDH* gene. Improvement is significant and usually rapidly appreciable on EEG. Treatment is life-long, and the usual dose of pyridoxine is around 15 mg/kg/day up to 500 mg/day. Learning difficulties, particularly language, seem to be a common complication of early-onset pyridoxine-dependent epilepsy. Variants of the disorder that respond to folinic acid instead of, or in addition to, pyridoxine have also been described, as well as atypical cases with long symptomatic periods or presenting later in infancy (i.e., weeks or months following birth up to three years of age).

PNPO, or pyridox(am)ine phosphate oxidase, deficiency is a distinct disorder involving refractory seizures responsive not to pyridoxine but to its biologically active form, pyridoxal-5-phosphate (PLP). This disorder is due to a defect in the enzyme PNPO, which synthesizes PLP from precursors pyridoxine-P and pyridoxamine-P. Patients may present prenatally with fetal seizures and premature birth and if untreated can progress to status epilepticus and death. Laboratory and genetic testings are available to confirm these diagnoses. It is treated by administering pyridoxal phosphate at a dose of 10–50 mg/kg/day.

Nonketotic Hyperglycinemia

This disorder of defective glycine degradation presents in the neonatal period with lethargy, hypotonia, hiccups, ophthalmoplegia and disturbance of other vegetative functions of the brainstem. As the coma deepens, apnea and frequent, segmental, myoclonic jerks develop. Over the next few months, severe refractory epilepsy develops, with myoclonus as the initial major seizure type but evolving into infantile spasms or partial motor seizures. Severe mental retardation and tetraplegia also become evident. In the first days and weeks, the EEG shows no normal background activity, but bursts of epileptic sharp waves (so-called burst suppression pattern), changing to high voltage slow activity, and then to hypsarrhythmia by around three months if the infant survives. The diagnosis is suggested by an increased glycine concentration in all body fluids and by the demonstration of an elevated CSF to plasma glycine ratio (> 0.08); it can be confirmed by a decreased activity of the hepatic glycine cleavage system and mutation analysis. MRI can be normal or show agenesis or hypoplasia of the corpus callosum.

Specific treatment is not available although lowering of glycine by administration of sodium benzoate does improve survival. In several patients, therapeutic trials with NMDA antagonists have been reported, with some effects on EEG and seizure frequency. Severe epilepsy is the rule in surviving children and is treated by conventional antiepileptic drugs. Valproic acid should not be used from a theoretical point of view, as it will further inhibit the hepatic glycine cleavage system.

Disorders of Creatine Metabolism

Among the disorders of creatine metabolism, guanidinoacetate methyltransferase (GAMT) deficiency is regularly associated with epilepsy, which is often refractory to conventional treatment. Creatine supplementation alone frequently leads to improvement. In some patients, reducing the toxic compound guanidinoacetate by dietary reduction of arginine and supplementary ornithine has been found to achieve epilepsy control. Infants can present with West syndrome, with atypical absences, astatic and generalized tonic-clonic seizures being common later on. Imaging findings can be normal even in untreated adults; but in some patients, basal ganglia signal abnormalities can be found. A diagnosis of GAMT deficiency may be suspected, by demonstrating increased excretion

of guanidino compounds in urine and when the prominent creatine and creatine phosphate peak is absent on proton magnetic resonance spectroscopy (1H-MRS) of the brain or cerebrospinal fluid.

LABORATORY INVESTIGATIONS

The goal of various laboratory studies, including biochemical testing, may be to determine the extent and severity of organ or tissue involvement, to classify a presumed inherited metabolic problem according to the aspect of metabolism involved and to establish a specific diagnosis. The tests should proceed from simple, widely available screening tests to specific, definitive costlier second-line investigations.

The screening tests include hemogram to pick-up leukopenia or thrombocytopenia that may be associated with organic acidemia, estimation of liver and renal functional tests. All children with suspected IEMs should have frequent glucose monitoring, estimation of electrolytes, arterial lactate, arterial blood gases, ammonia and ketone bodies. Simple urine tests like dinitrophenylhydrazine test (DNPH), ferric chloride, silver nitroprusside test, Rothera test for ketone bodies, Benedict's test for reducing sugars and Seliwanoff test for fructosuria when positive can give vital clues to diagnosis and guide further specific tests. They can also guide appropriate treatment pending the results of the definitive second-line investigations.

In children who show some abnormalities in the routine screening tests or in whom the suspicion of IEM is very high second-line investigations can be ordered **(Box 4)**.

Points to Remember before Sending Samples

Sample should be collected before specific treatment is started or feeds are stopped as results may be falsely normal, if the child is off feeds. Samples like serum ammonia and lactate should be immediately tested. Lactate preferably arterial and 2 hours after feeding. Gas chromatography/mass spectrometry (GC/MS) is a test used mainly for nonpolar substances like organic acids and tests like high performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) is good for polar substances like amino acids and orotic acids. Depending on the clinical suspicion, appropriate tests should be ordered.

Role of MRI and MR Spectroscopy

Neuroimaging findings can aid in reaching a proper and prompt diagnosis of inborn errors of metabolism for an effective treatment and to obtain baseline studies to monitor the disease. These can at times be very conclusive when a paucity of the facilities and financial constraints prevent or delay the enzymology, histology and molecular studies. Neuroimaging can thus be an eye opener

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BOX 4 Investigations for neurometabolic disorders

1. *Brain imaging:* Magnetic resonance imaging (MRI) is preferred to computer tomography (CT) scan of brain
2. Electrophysiological studies like brainstem evoked response audiometry (BERA), visual evoked potentials (VEP), somatosensor evoked potentials (SSEP), nerve conduction studies and electromyography (EMG)
3. Radiographs of hands, chest, spine
4. *Plasma aminoacidogram:* Thin layer chromatography (TLC) screening, quantitative if abnormalities are found
5. Urinary aminoacidogram by TLC/paper chromatography
6. HPLC (High performance liquid chromatography)
7. Tandem mass spectroscopy (TMS)
8. Urinary gas chromatography/mass spectroscopy (GC/MS)
9. Urinary MPS screening test
10. Urinary oligosaccharide screening test.

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in the unexplained cases. Pattern of involvement of basal ganglia, dentate nucleus, white matter and cerebral/cerebellar atrophy provided important clues for the diagnosis. IEM may be associated with characteristic imaging findings.

- Diffuse cortical migration and sulcation abnormalities are seen in Zellweger syndrome.
- Agenesis of the corpus callosum is seen in pyruvate decarboxylase deficiency, Menkes disease and nonketotic hyperglycinemia.
- Brainstem and cerebellar edema are seen in Maple syrup urine disease.
- Subdural hematomas and frontotemporal atrophy giving characteristic 'bat-wing' appearance suggest glutaric aciduria.
- 3-Methylglutaconic aciduria type I is a rare inborn error of leucine catabolism that has extensive white matter disease.
- *Pyruvate dehydrogenase deficiency:* MRI of the brain shows complete or partial agenesis of the corpus callosum, heterotopic gray matter, the absence of the medullary pyramids and the abnormal inferior olives, hydrocephalus and cerebellar dysplasia.
- *Leigh's disease:* shows bilateral, symmetric, focal hyper-intensities in the basal ganglia, the thalamus, the substantia nigra, and the brainstem nuclei at various levels on the T2-weighted MRI images due to spongiform changes and vacuolation in the affected brain structures.

MR Spectroscopy

Magnetic resonance spectroscopy (MRS) provides a window on the intracellular metabolic events that occur in various neurometabolic disorders thereby giving vital clues to the diagnosis. MRS is a clinically useful, noninvasive tool for identifying the biochemical state of the CNS. MRS can be complementary to MRI by giving chemical pathology of MRI detected lesions and there is evidence that MRS may also detect abnormalities not revealed by MRI. MRS offers valuable information for the individual patient for his/her diagnosis and therapy when it is integrated fully into the clinical setting.

Metabolites measured with 1H-MRS include N-acetyl-aspartate (NAA), a neuronal marker; creatine (Cre) composed of phosphocreatine and creatine, which are bioenergetic metabolites; choline-containing compounds (Cho), including free choline and phosphoryl and glycerophosphoryl choline that are released during membrane disruption; lactate (Lac), which accumulates in response to tissue damage or anaerobic glycolysis; and other metabolites only seen when acquired with short echo time sequences, such as the neurotransmitters glutamate and immediately formed glutamine (Glx) and myoinositol (mI or Ins), an osmolyte and astrocyte marker.

Characteristic Patterns in Important Neurometabolic Disorders

a. In Canavan disease, MRS shows marked elevation of the NAA peaks. In addition to an elevated NAA peak, patients with Canavan disease have abnormally increased NAA/Cre and NAA/Cho ratios.
b. *Creatine deficiency:* Proton MRS shows reduced or absent creatine peak.
c. Pyruvate dehydrogenase (PDH) deficiency shows an elevated level of pyruvate at the 2.37 ppm.
d. *Leigh's disease:* In Leigh's disease and other mitochondrial disorders, MRS reveals an abnormally high lactate peak and a decreased NAA peak in the basal ganglia and occipital gray matter. This is demonstrated in MR spectroscopy as peak at 1.33 ppm.
e. *Adenoyl succinate lyase deficiency:* There is a characteristic accumulation of succinyladenosine (S-Ado) in the tissue and

in the body fluids. The in vivo proton MRS measurements show a prominent signal at the 8.3 ppm in the gray and white matter brain regions of all the patients that corresponds to the accumulated S-Ado.

f.   In phenylketonuria, elevated phenylalanine levels can be seen with MRS of the brain.

g.   *Nonketotic hyperglycinemia:* Proton-MR spectroscopy detects increased intracerebral levels of glycine, lactate, and creatine.

Role of Genetic Studies

Neurometabolic disorders are the inherited disorders with majority of them having autosomal recessive inheritance. Because they are common in consanguineously married couples, there is a risk of recurrence in the next sibling and genetic counseling is an important aspect while treating neurometabolic disorders. The role of pediatrician does not end at just diagnosis and treatment of the index child. The causative gene for most disorders is known and a genetic diagnosis should always be attempted in all cases. This will help in confirming the diagnosis in a given child and gives fool-proof technique for prenatal diagnosis. Prenatal diagnosis of neurometabolic disorders based on amniotic fluid analysis for metabolites are not very sensitive and specific.

TREATMENT

Comprehensive management of IEM includes both dietary treatment and pharmacotherapy. It is usually implemented by an interdisciplinary team consisting of metabolic pediatrician, pediatric intensivist, dietitian, nurses, occupational therapist and physiotherapist. There are certain simple principles that need to be followed while we manage a case of IEM.

1.   Treatment may have to be instituted empirically without a specific diagnosis
2.   Reduce formation of toxic metabolites by decreasing substrate availability (stopping feeds and preventing endogenous catabolism)
3.   To provide adequate calories
4.   To enhance excretion of toxic metabolites
5.   To institute co-factor therapy for specific disease and also empirically if diagnosis is not formed.

Management at tertiary center consists of cardiorespiratory support; nonresponse or worsening on supportive therapy: peritoneal dialysis, hemodialysis, exchange transfusion to get rid of toxic metabolites; specific therapy—special diets, vitamins; and genetic counseling and prenatal diagnosis.

Pharmacological Treatment

Detailed treatment of metabolic disorders is described in Section 3. We discuss a few pertinent points here:

- *Replacement of product*: This consists of reaction product replacement like creatine monohydrate in guanidinoacetate methyltransferase deficiency, arginine in argininosuccinic aciduria and L-serine in 3-phosphoglycerate dehydrogenase deficiency.
- Enzyme replacement therapy (ERT).
- Co-factor replacement therapy.
- Gene transfer therapy (Still experimental).

Co-factor replacement therapy It forms an important part of treatment of IEM. Co-factors are the vitamins and minerals that affect the catalytic properties of many enzymes. Vitamin dependency states result due to mutations in the enzyme protein that affects utilization or binding of the vitamin or mineral co-factor. Several hundred times the physiological requirement of vitamins and minerals are required to treat the vitamin dependency states. **Table 3** shows the various co-factors that are helpful in different IEMs.

Dietary therapy Restrict substrates which accumulate (form toxic metabolites) like phenylalanine in phenylketonuria. Replace essential nutrients that are not produced due to block in the metabolic pathway like cysteine in homocystinuria. Diet should be nutritionally adequate for growth and development. Dietary therapy should be started as early as possible. Some restriction is required throughout life in most situations.

IN A NUTSHELL

1.   Neurometabolic disorders have a varied presentation affecting the neurological system and other organ systems.
2.   Though individually rare, collectively they are not uncommon. A high index of suspicion is required for timely diagnosis and good outcome.
3.   Simple biochemical tests and neuroimaging give vital clues for a possibility of neurometabolic disorders that could be followed by definitive diagnostic tests like metabolic tests like mass spectrometry (tandem mass or urine gas chromatography) or genetic studies.
4.   Protocol-based intensive management is required for these disorders for a good final outcome.
5.   Always offer genetic counseling and prenatal diagnosis.

MORE ON THIS TOPIC

Clarke JTR. A clinical guide to inherited metabolic diseases. 3rd ed. Cambridge: Cambridge University Press; 2006.

Fernandes J, Saudubray JM, van den Berghe G, Walter JH. Inborn Metabolic Diseases—Diagnosis and Treatment. 4th ed. Medizin Verlag Heidelberg Germany: Springer; 2006.

Table 3 Co-factors for treating neurometabolic disorders

Co-factor	Disorders
• Thiamine	• Maple syrup urine disease, pyruvate dehydrogenase deficiency & complex I deficiency
• Riboflavin	• Glutaric aciduria type I and II, complex I deficiency
• Pyridoxine	• Homocystinuria, pyridoxine dependency, xanthurenic aciduria, primary hyperoxaluria type I
• Pyridoxal PO_4	• Pyridoxamine 5-phosphate oxidase deficiency
• Cobalamin	• Methylmalonic academia
• Folic acid	• Some cases of homocystinuria
• Folinic acid	• Hereditary orotic aciduria, methionine synthase deficiency, cerebral folate transporter deficiency, Kearns-Sayre syndrome
• Biotin	• Biotinidase deficiency, holocarboxylase synthetase deficiency
• Pantothenic acid	• 3-methylglutaconic aciduria type III
• Nicotinamide	• Hartnup disease
• Coenzyme Q_{10}	• CoQ_{10} deficiency, mitochondrial cytopathies
• Ascorbic acid	• Hawkinsuria, tyrosinemia type III
• Vitamin E	• Abetalipoproteinemia, glutathione synthetase deficiency
• Tetrahydrobiopterin	• Disorders of BH_4 synthesis, BH_4 responsive forms of PKU

Chapter 42.26
Neurodegenerative Disorders
Naveen Sankhyan

Neurodegenerative disorders (NDDs) are characterized by loss of acquired milestones. The manifestations of neurodegeneration vary with age and depends on the area of neuraxis preferentially involved. The outcome of most childhood NDDs is dismal but a proper diagnosis is essential for genetic counseling, prenatal diagnosis and prognostication.

EPIDEMIOLOGY

The true burden of NDDs in India remains unknown, though most of the common NDDs have been reported from India. A recent single center laboratory-based study reported sphingolipidoses as the most frequently occurring lysosomal storage disorder followed by mucopolysaccharidoses. Disorders like megalencephalic leuko-encephalopathy with subcortical cysts have been reported to have high incidence in specific populations in India.

PATHOGENESIS

For most disorders, the precise process by which the abnormal enzyme activity or abnormal metabolite accumulation causes brain damage is yet be defined. Both intrinsic and extrinsic factors are thought to be involved in the pathogenesis. The basis for most neurodegeneration is a gene defect, usually causing a faulty gene product (mostly an enzyme). Due to lack of enzyme activity there is either a lack of essential products or transporters or an accumulation of toxic metabolites. The underlying gene defect either affects—all the neurons or functionally-related neurons. Certain disorders may preferentially involve part of the neuron structure, e.g., axon, myelin, etc. Exogenous factors that can aggravate neuronal injury include prolonged fasting, high protein load, fever, hypoglycemia, etc.

APPROACH TO DIAGNOSIS

Rule Out Treatable Causes and Pseudoregression

Though pseudoregression is only apparent after the complete history and examination, its evaluation is importance. We need to identify these causes to treat them early and to avoid unnecessary investigations, and allay parental anxiety. Regression can occur due to poorly controlled seizures, over-medication with anticonvulsants, intercurrent systemic illness, nutritional deficiency states and secondary neurological problems. In a static encephalopathy, conditions that can result in a loss of milestones are; development of joint contractures, seizures, or a new onset of movement disorder. Disabled children are also at risk for depression or other emotional problems. These psychological problems can lead to memory, mood changes and behavioral changes which may be interpreted as a sign of neuroregression. Loss of abilities can also occur due to nonhereditary treatable disorders like progressive hydrocephalous, hypothyroidism, retroviral infection, psychosocial stress or depression. In some parts of India, infantile tremor syndrome is common and infants who are predominantly breastfed suffer from vitamin deficiency state and present with typical cutaneous pigmentation, cognitive regression with or without tremors.

History and Examination

A detailed history is aimed at ascertaining the age of onset, and the areas of development affected. The disorder may predominantly affect motor milestones, vision, hearing, or cognition. The spheres of development involved indicate the possible areas in the neuro-axis and give a clue to the differential diagnosis **(Table 1)**. Since almost all disorders causing neuroregression are hereditary a family history of three generations is important to identify the mode of inheritance and to identify others at risk or mildly affected individuals. Certain findings in general physical and systemic examinations give an indication to the nature of disorder **(Table 1, Figs 1 and 2)**. After a detailed history and examination, we generally get a fair idea about the possible distribution of the pathological process within the nervous system **(Table 2)**. We would also know whether we are dealing with a pure neurological disorder or other organ systems are involved as well.

The overall goal is to arrive at a reasonable syndromic diagnosis (as below) to guide further testing. The age and the syndromic diagnosis then helps us to narrow down the differentials based on the most dominant positive and negative clinical features. Frequently, findings from the initial investigations also aid in considering differentials.
1. Gray matter degenerations
2. White matter degeneration—Leukodystrophies
3. Progressive ataxias
4. Basal ganglia disorders
5. Multisystem disorders with neuroregression

Regression in a Child below Two Years (Flow chart 1)

Disorders that have very early onset often have profound and rapid effects on development. The child frequently has delayed

Table 1 Clinical features of gray and white matter diseases

Features	*Gray matter*	*White matter*
Loss of social interaction and cognitive abilities	Early	Late
Seizures	Early and prominent	Late
Retinitis pigmentosa	May be present	Absent
Primary optic atrophy	Rare	May be seen
Primary neuropathy	Rare	May be seen
Imaging (MRI)	Cortical atrophy, abnormalities in basal ganglia, cerebellum (in those with specific involvement of these structures)	Clearly identifies abnormalities in white matter [may yield specific diagnostic findings]
Electroretinogram (ERG)	May be abnormal	Normal
Visual evoked response (VER)	May be abnormal	Normal
Brainstem auditory evoked responses (BAER)	Usually normal	Abnormal
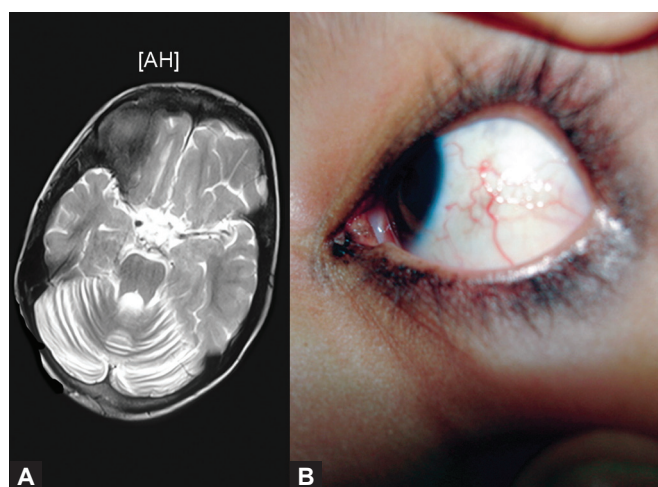
Figures 1A and B Axial T2W MR scan showing cerebellar atrophy (A) and extensive conjunctival telangiectasias in a child with Ataxia telangiectasia (B)

milestones and then regresses further. Often due to lack of any clear acquired milestones, the loss of milestones may be difficult to appreciate. Most commonly, the baby would not have visual fixation, social interaction or any head control or voluntary reaching. Other common symptoms include seizures, irritability or lethargy, hypotonia, feeding difficulties and/or vomiting, and/or failure to thrive.

Beyond the first year of life, the loss of milestones becomes easier to identify. Loss of motor milestones is often an early sign of neurodegeneration in this group. The loss of motor abilities may result from corticospinal, cerebellar, extrapyramidal or motor unit involvement. During the second year of life disorders with neuro-visceral storage (mucopolysaccharidosis and mucolipidosis) also begin manifesting with gradually increasing dysmorphism, skeletal abnormalities and cognitive decline. Pure neurological deterioration with prominent seizures and vision loss is evident at this age in children with neuronal ceroid lipofuscinosis (NCL). Yet another group of children presents with recurrent neurological deterioration interspersed with apparent recovery (organic aciduria, mitochondrial disorders, urea cycle disorders, etc.). Disorders like Rett syndrome are characterized by peculiar loss of purposeful hand movements and acquired microcephaly in girls.

Neuroregression Beyond 2 Years and in Adolescence (Flow charts 2 and 3)

In children beyond the age of two years the onset of NDDs is easier to identify. The traditional clinical distinction between the phenotypes of NDDs like white matter, gray matter disorders, and cerebellar degenerations are much evident now. The mimickers of NDDs in older children include disorders previously discussed and also SSPE (subacute sclerosing pan-encephalitis), presenting with behavioral changes, cognitive deterioration with or without myoclonic jerks. Another important aspect of disorders presenting later in childhood is the wide variation in symptomatology. The variability is evident in both recessively (Wilsons disease, GM1, GM2 gangliosidosis) and dominantly inherited disorders (Spinocerebellar ataxia, Huntington's disease).

INVESTIGATIONS

Imaging

A high resolution MR imaging with spectroscopy (MRS) is the desirable investigation. In certain children, it may provide a diagnostic clue, e.g., Pantothenate kinase-associated neuro-degeneration (PKAN) with *eye of tiger* sign in globus pallidi **(Fig. 3)**, adrenoleukodystrophy **(Figs 4A and B)**, and glutaric aciduria **(Fig. 5)**. MRS helps in diagnosis of certain disorders such as Canavan, mitochondrial encephalopathies **(Figs 6A to C)**, and creatine deficiency disorders. Neuroimaging also guides to further work-up of a child by showing suggestive findings [Wilson disease, metachromatic leukodystrophy **(Fig. 7)**] or excluding certain conditions which have characteristic findings.

Plain radiographs of bones are important in suspected neuro-visceral storage including mucopolysaccharidosis, mucolipidosis, gangliosidosis, fucosidosis and others **(Figs 8A and B)**.

Biochemical Tests

Urine and blood assay for plasma ammonia, blood lactate and pyruvate, plasma amino acids, urine organic acids, blood acylcarnitine guide the evaluation of child with suspected neurometabolic disorder.

Electrophysiological Tests

These include VEP, BAER, NCS, EEG, EMG, and somatosensory evoked potentials. These may help delineate the extent of central and peripheral nervous system involvement in the patient.

Figures 2A and B Axillary excoriated rash (A) and alopecia and scalp seborrhea (B) in a child with biotinidase deficiency

Table 2 Some clinical pointers in hereditary neurodegenerative disorders

Organ/features	Abnormality	Disorders
Head	Microcephaly	NCL, Krabbe disease, Rett syndrome
	Macrocephaly	MPS, Alexander, Canavan, GM1 gangliosidosis, Tay-Sachs disease, MLSC
Hair	Alopecia	Biotinidase deficiency
	Pigmentary changes	PKU, Menkes
	Wooly, kinky hair	Menkes
Skin	Rash	Biotinidase, holocarboxylase deficiency
	Subcutaneous nodules	Farber disease
	Angiokeratomas	Fabry disease
	Fat pads, focal atrophy	Congenital disorders of glycosylation
	Hyperpigmentation	Adrenoleukodystrophy
Eyes	Cataract	Galactosemia, Zellweger, Wilson disease
	Retinitis pigmentosa	Peroxisomal disorders, NCL, mitochondrial encephalomyopathies, MPS, PKAN, ABLP
	Cherry red spot	Tay-Sachs disease, Niemann-Pick, GM1 gangliosidosis
	Optic atrophy	NCL, MLD, Krabbe, Canavan, GM2 gangliosidosis
Ears	Deafness	MPS, ALD, Mitochondrial disorders
	Hyperacusis	Krabbe, Tay-Sachs
Abdomen	Hepatosplenomegaly	MPS, GM1 gangliosidosis, Gaucher, Niemann-Pick
	Hernia	GM1 gangliosidosis, MPS
Nervous system	Peripheral neuropathy	MLD, Krabbe, Mitochondrial disorders, Niemann-Pick
	Hydrocephalous/raised Intracranial pressure	MPS, Infantile Alexanders
Cardiac	Cardiomyopathy	FAOD, mitochondrial disorders, Friedreich ataxia, AVED, Pompe disease
	Valvular defects	MPS, Zellweger, Fabry

Abbreviations: NCL, neuronal ceroid lipofuscinosis; MPS, mucopolysaccharidosis; PKU, phenylketonuria; PKAN, pantothenate kinase-associated neurodegeneration; ABLP, abetalipoproteinemia; MLD, metachromatic leukodystrophy; ALD, adrenoleukodystrophy; FAOD, fatty acid oxidation defects; AVED, ataxia with vitamin E deficiency; MLSC, megalencephalic leukodystrophy with subcortical cysts

Flow chart 1 Approach to progressive neurological deterioration in a child less than 2 years of age
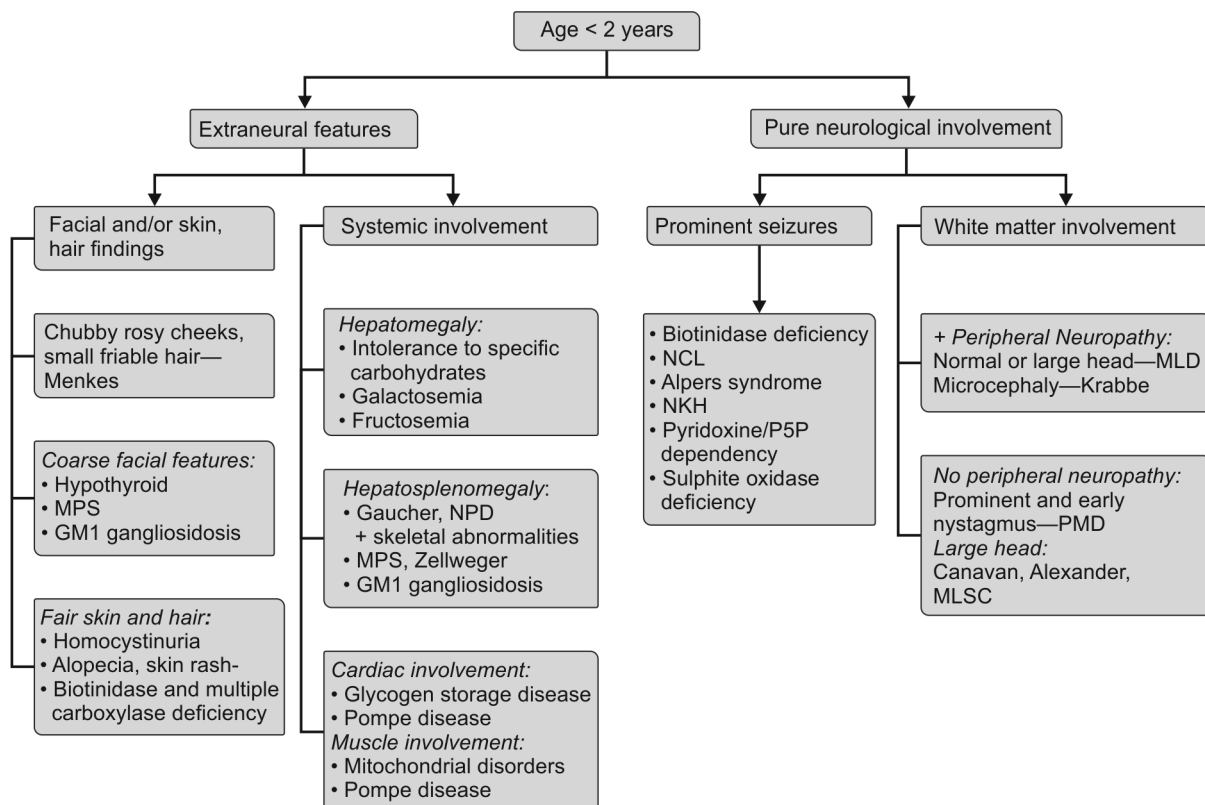
Abbreviations: MLD, metachromatic leukodystrophy; PMD, Pelizaeus-Merzbacher disease; NCL, neuronal ceroid lipofuscinosis; MLSC, megalencephalic leukodystrophy with subcortical cysts; MPS, mucopolysaccharidosis; NPD, Niemann-Pick disease; P5P, pyridoxal 5 phosphate; NKH, Nonketotic hyperglycinemia.

Flow chart 2 Approach to progressive neurological deterioration in two to five years age group

Primary involved area of CNS on history and examination →

- White matter disorder → MLD, ALD
- Extrapyramidal syndrome → PKAN / Lesch-Nyhan / Glutaric aciduria I
- Progressive myoclonic epilepsy/gray matter degeneration → NCL / MERRF
- Ataxia → Ataxia telangiectasia / Respiratory chain disorders / Early onset SCA
- Gray matter and coarseness → MPS / Mucolipidosis
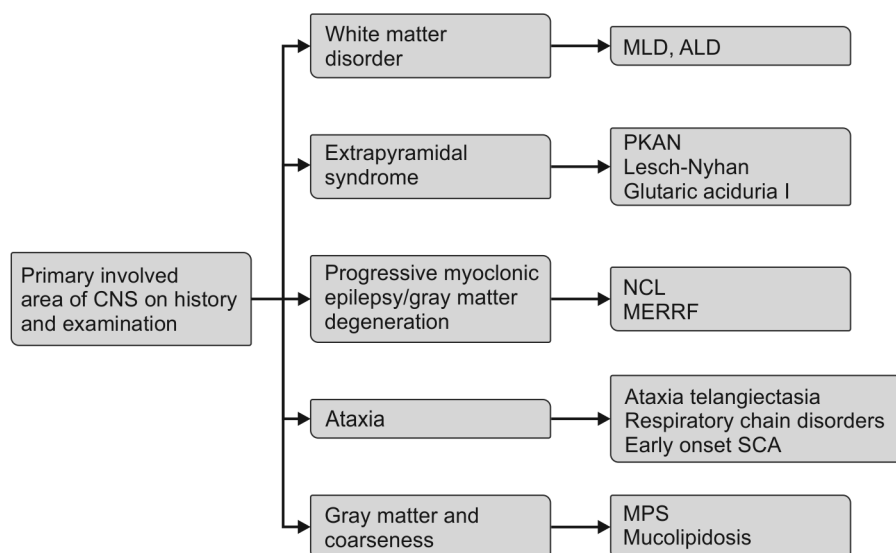
Abbreviations: MLD, metachromatic leukodystrophy; NCL, neuronal ceroid lipofuscinosis; ALD, adrenoleukodystrophy; MERRF, myoclonic epilepsy with ragged red fibers; PKAN, pantothenate kinase-associated neurodegeneration; SCA, spinocerebellar ataxia

Flow chart 3 Approach to progressive neurological deterioration in five to fifteen years age group

Primary involved area of CNS on history and examination →

- White matter → ALD, MS
- Extrapyramidal syndrome → Wilson disease / PKAN / Huntington chorea / Progressive hereditary Dystonias
- Progressive myoclonic epilepsy/gray matter degeneration → SSPE / NCL / MERRF
- Ataxia → Friedreich ataxia / Spinocerebellar ataxias / AVED / Abetalipoproteinemia
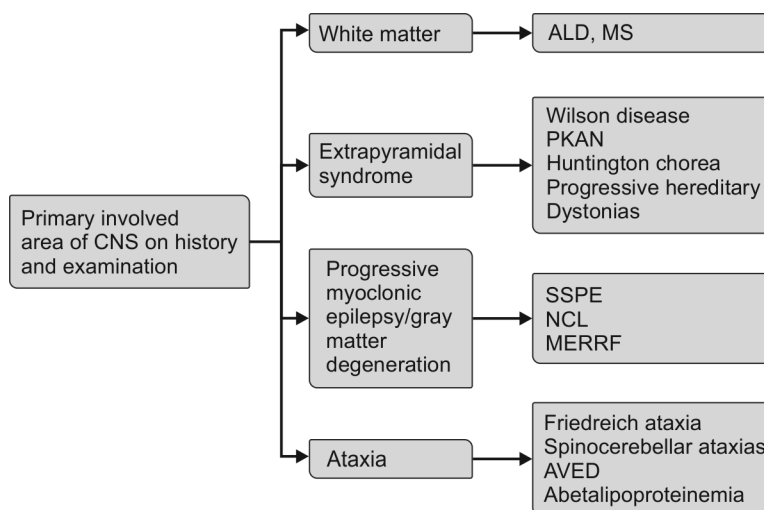
Abbreviations: ALD, adrenoleukodystrophy; MS, multiple sclerosis; SSPE; subacute sclerosing panencephalitis; MERRF, myoclonic epilepsy with ragged red fibers; PKAN, pantothenate kinase-associated neurodegeneration; NCL, neuronal ceroid lipofuscinosis; AVED, ataxia with vitamin E deficiency.

Hematology and Histopathology

Peripheral smear provides supportive evidence in the form of vacuolated lymphocytes (NCL, Niemann-Pick disease, Pompe disease, GM1 gangliosidosis) or acanthocytes (PKAN, abetalipo-proteinemia, neuroacanthocytosis). Bone marrow examination demonstrates storage cells in Niemann-Pick disease, and Gaucher disease. Conjunctival, skin, and rectal biopsy help in the diagnosis of neuronal ceroid lipofuscinosis. Hair microscopy is diagnostic for Menkes disease **(Figs 9A and B)**.

Specific Investigations

These are done based on clues from preceding investigations; Serology for HIV, SSPE; Urine copper and serum ceruloplasmin for Wilson disease; Urine MPS for mucopolysaccharidosis; Enzyme analysis for lysosomal storage disorders, biotinidase deficiency; VLCFA and plasmalogen levels for peroxisomal disorders; and Mutation testing if the diagnosis is certain and the test is available.

TREATMENT

The first priority is to identify treatable causes of neuroregression like hydrocephalous, HIV infection, hypothyroidism, lead toxicity, etc. Specific treatment is available for many neurodegenerative disorders **(Table 3)**. Newer treatment options are now available. The child should be referred to a center with treatment facilities to ensure timely intervention.
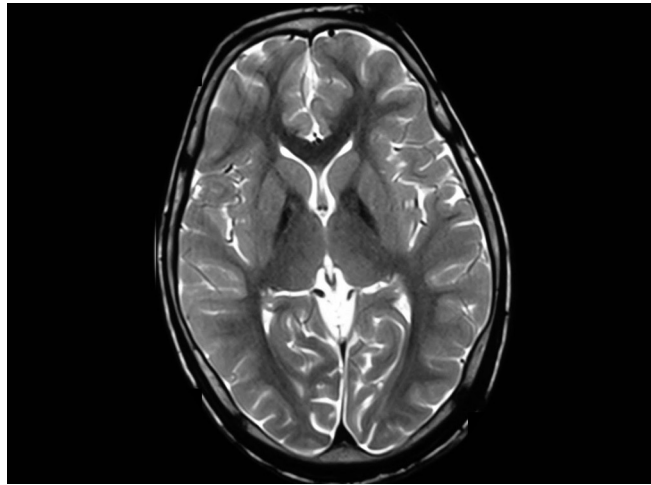
Figure 3 Bilateral symmetrical hypointensities in the globus pallidi on axial T2W images in a child with PKAN
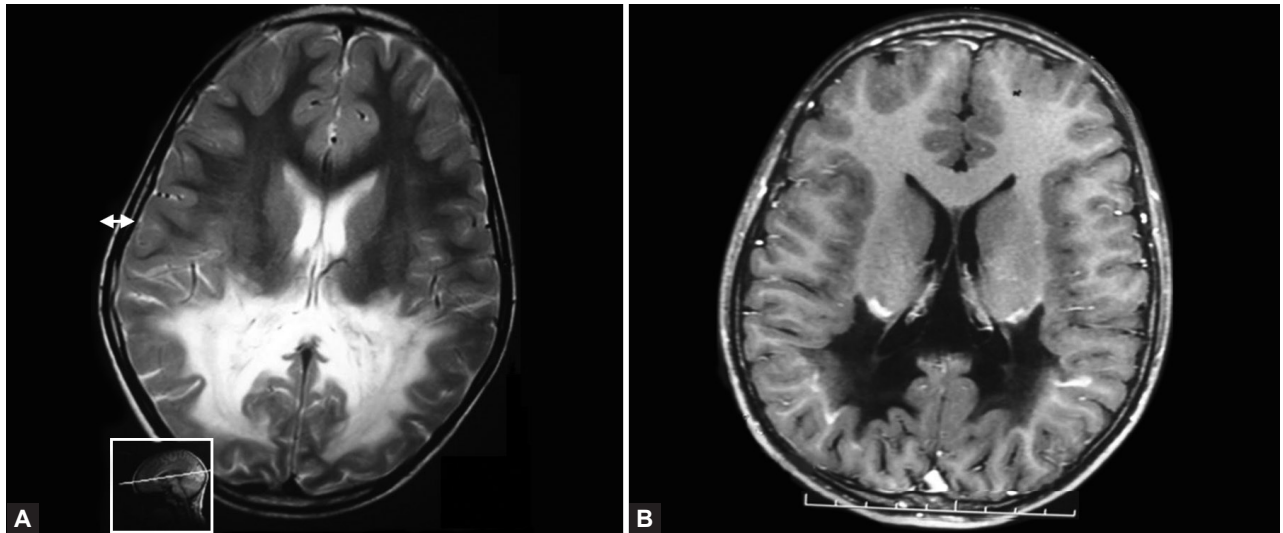
Figures 4A and B Axial MR scan of the brain, T2W images (A) showing posteriorly dominant, symmetrical, white matter hyperintense signal changes in a child with adrenoleukodystrophy. Note the characteristic peripheral contrast enhancement on postcontrast T1W image (B)
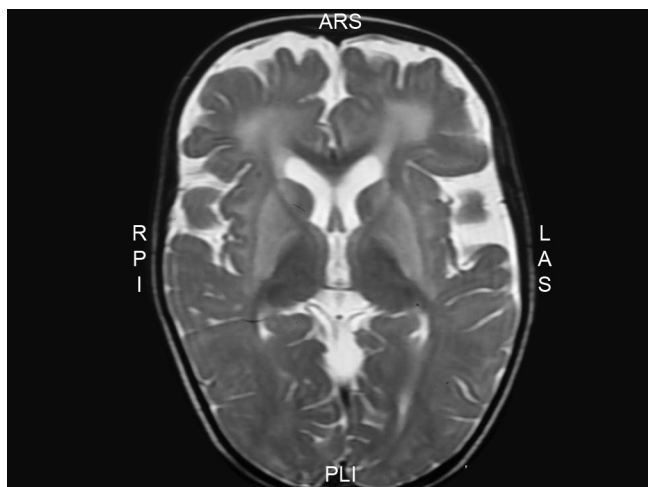
Figure 5 T2W MR scan of brain axial sections showing bilateral striatal hyperintensities, frontal white matter hyperintensities and frontotemporal atrophy with open operculam in a child with glutaric aciduria type 2
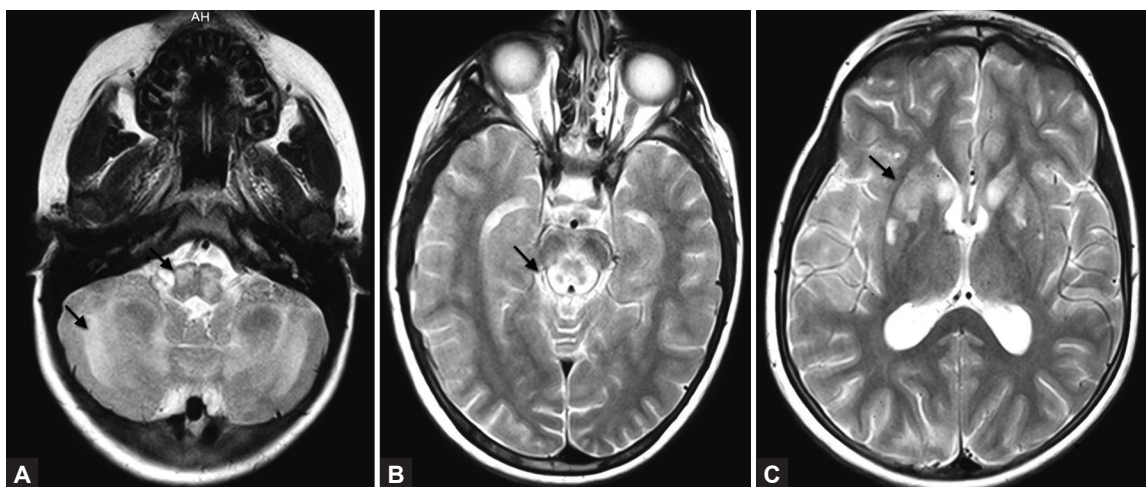
Figures 6A to C Axial T2W MRI in a child with Leigh's syndrome showing hyperintense signal changes (black arrows) in the medulla, cerebellum (A), midbrain (B), and bilateral basal ganglia (C)
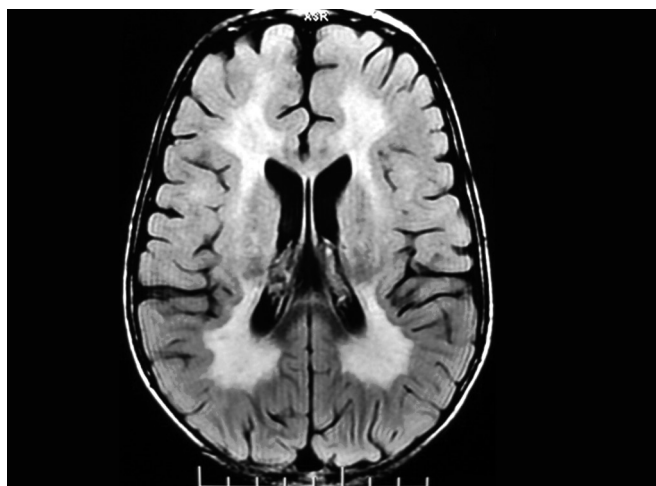
Figure 7 Symmetrical hyperintensities on axial FLAIR MR images in periventricular white matter of a child with MLD
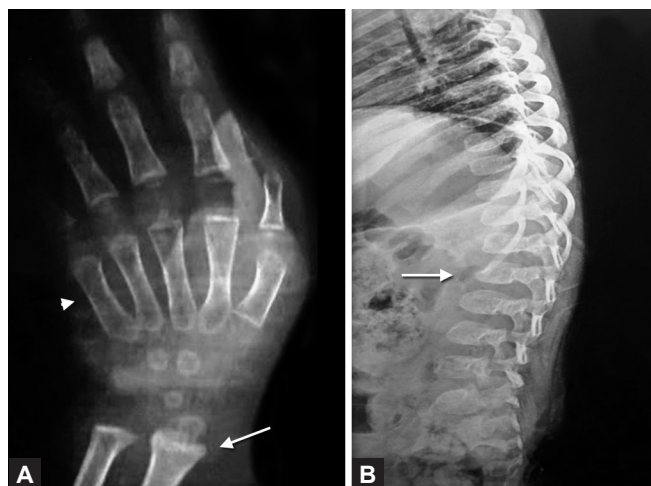
Figures 8A and B Wrist X-ray (A) showing epiphyseal changes (white arrow), and proximally tapered carpal bones (white arrowhead), the vertebral bodies show anteroinferior beaking in a child with mucopolysaccharidoses
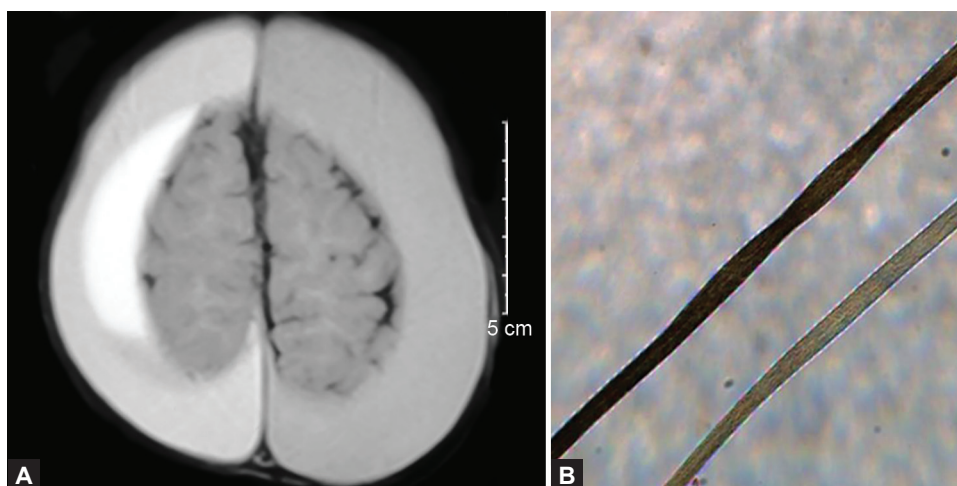
Figures 9A and B Marked brain atrophy with subdural collections (A) and microscopy of the hair showing pili torti in a child with Menkes disease

Table 3 Few examples of treatment in neurodegenerative disorders

Disease	Therapeutic agent
Gaucher disease	Enzyme replacement, Miglustat
Fabry disease	Enzyme replacement
Attenuated variants of MPS I	Enzyme replacement
Pompe disease	Enzyme replacement
Ataxia (CoQ deficiency)	Coenzyme Q10
Ataxia with vitamin E deficiency	Vitamin E
Minimally symptomatic X-linked adrenoleukodystrophy	Bone marrow transplant
MPS 1H-Hurler disease	Bone marrow transplant
Glycogen storage disease	Liver transplant
Glutaric aciduria–II, Biotinidase deficiency	Co-factor replacement

Supportive Measures

Supportive treatment adds significantly to the quality of life of a child with NDD. Measures to reduce spasticity, control seizures, control pain, improve nutrition, prevent constipation, prevent bed sores, and to enhance mobility all contribute to the quality of life of the patient and indirectly to the quality of life of the parents and any unaffected siblings.

PROGNOSIS

The prognosis in neurodegenerative disorders depends on the underlying disorder. The prognosis of a NDD should be discussed only after confirming the diagnosis. While prognosticating the variability in disease progression should be kept in mind. In general an earlier onset of disease predicts a poorer outcome. However, several late onset diseases can also rapidly progress, e.g., adrenoleukodystrophy.

PREVENTION

All efforts should be taken to establish an accurate diagnosis and offer prenatal diagnosis to prevent further children being affected by the same disease. The diagnosis may also help identify pauci or presymptomatic siblings or other family members who may benefit from early therapy, e.g., zinc therapy in Wilson disease. It would be wise to refer the parents for prenatal diagnosis to an equipped center before they plan any future pregnancies.

SELECTED NEURODEGENERATIVE DISORDERS

WHITE MATTER NEURODEGENERATIVE DISORDERS

Krabbe Disease

Globoid cell leukodystrophy or Krabbe disease is an autosomal recessive disorder caused by the deficiency of a lysosomal enzyme galactosylceramidase. It is an early onset, rapidly progressive and invariably fatal disease of infants. Late onset childhood and adult forms have also been described. In the most common form the *early infantile type*, onset is between 3 months and 6 months of age. The disease begins with generalized hyperirritability, hyperesthesia, episodic fever, over response to stimulation. This progresses rapidly to a stage of severe motor and mental deterioration, deep tendon reflexes (DTRs) are at first increased, then decreased, optic atrophy, decreased head growth are soon evident. The disease progresses to a state of burn out leaving the child decerebrate and blind.

In the late infantile type the child is normal during first year, then develops ataxia, weakness, spasticity, dysarthria, visual loss with optic atrophy. The disease course is slower compared with the infantile variety.

In the Juvenile onset (4–19 years) and adult onset (> 20 years) the disease manifests as slowly progressive spastic tetraplegia, optic nerve pallor, pes cavus, and sensory motor demyelinating neuropathy. Mental functions are preserved in around 50% of affected the patients. The hallmark of this disease on investigations is the presence of demyelinating polyneuropathy and raised CSF proteins. In early onset disease, MR imaging demonstrates high signal intensity in periventricular white matter with sparing of peripheral white matter in early stage. Signal abnormality in hilus of dentate nucleus, cerebellar WM and pyramidal tracts in the brainstem in an infant of few months are characteristic of Krabbe disease.

Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a X-linked hypomyelinating leukodystrophy. It is caused by the deficiency of proteolipid protein (PLP), an important myelin protein. PMD exhibits a broad clinical continuum. The most severe variant being the connatal variant of PMD, and the least severe being the pure form of Spastic Paraplegia Type 2. Classic PMD begins in first months of infancy with abnormal eye movements; rapid, irregular, small or large amplitude oscillations either vertical or horizontal. This is followed by slow development of spasticity, ataxia and involuntary movements. With disease progression, optic atrophy and seizures occur. Mental abilities usually are relatively preserved. Children with connatal form of PMD present shortly after birth and have an aggressive clinical course. Patients develop severe hypotonia, extrapyramidal signs, stridor and feeding difficulties. Death occurs within few months to years. X-linked form of spastic paraplegia that occurs either as a pure form, consisting of a slowly progressive paraplegia involving only lower limbs; or as a complicated form, in which spastic paraplegia occurs along with other features of PMD like nystagmus, dysarthria and ataxia.

Alexander Disease

Alexander disease is caused by mutation in the gene encoding glial fibrillary acidic protein. This condition begins in the first year of life with intellectual deterioration, macrocephaly, spasticity and seizures. Juvenile and adult forms also occur. The juvenile form often has no macrocephaly but bulbar and pseudobulbar signs of swallowing and/or speech difficulty occur frequently. The adult onset form has variable clinical features, and can resemble multiple sclerosis. Ataxia, quadriparesis, palatal myoclonus and other brainstem signs are prominent.

MRI shows diagnostic findings. It reveals extensive white matter changes with frontal predominance, a periventricular rim of altered signal intensity. The peripheral white matter is affected early in course of the disease. In late stages, cysts may develop. Bilateral, symmetrical, frontal white matter involvement involving the U-fibers in a macrocephalic patient is quite specific for Alexander disease, particularly if it extends posteriorly to involve the caudate heads.

Canavan Disease

Canavan disease is an autosomal recessive disorder characterized by spongy degeneration of white matter of the brain. It is caused by deficiency of enzyme aspartoacylase, leading to excessive

accumulation of N-acetyl aspartic (NAA) acid in the brain, especially in the white matter, with massive urinary excretion of NAA. The onset of this disease is between 3 months and 6 months of age with progressive macrocephaly, severe hypotonia, and persistent head lag. Later these children become hyper-reflexic and hypertonic. Seizures and optic atrophy occur. Most patients die in first decade of life. Neuroimaging shows diffuse symmetric abnormalities of cerebral white matter, including early involvement of subcortical white matter without any lobar predominance Globus pallidi involvement in association with diffuse white matter disease including the subcortical, deep, and periventricular regions suggests a diagnosis of Canavan disease. Magnetic resonance spectroscopy demonstrates a significant elevation of NAA peak and increase in NAA-to-choline ratio in cerebral white matter. The urinary and blood NAA levels are elevated.

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder of myelin metabolism caused by deficiency of arylsulfatase A, or exceptionally, to a defect of nonenzymatic protein activator SAP 1. MLD most often occurs in the late infantile period usually in the second year of life, but less aggressive forms appear in late childhood and adolescence, and in adults. The *Late Infantile form* is the most frequent form of MLD, representing 60–70% of all cases. It is usually manifest between 1 and 2 years of age, with gait disturbance, ataxia, or weakness. Hypotonia may be the only and earliest sign. The most striking clinical finding in this stage is the absence of deep tendon reflexes, because of peripheral nerve involvement. Nerve conduction velocities are markedly decreased suggesting demyelination. Briefly, during the early stages, the mental status is normal and there is no vision impairment. But soon the neuroregression progresses to cause decerebrate posturing, genu recurvatum, optic atrophy and loss of speech develop; seizures occasionally occur. Death usually occurs between the ages of 3 years and 7 years. In the juvenile form symptoms begin between 5 years and 10 years of age. Deterioration in school performance and personality changes may be herald the onset of the disease. This is followed by gait problems, urinary incontinence and dysarthria. During the terminal stages, episodes of decerebrate posturing and generalized tonic clonic seizures occur. Death occurs by mid-adolescence. The adult form of MLD presents with dementia between the 3rd and 4th decades of life. Abnormalities in memory, psychiatric features, and personality changes are prominent features. There may be accompanying corticobulbar, corticospinal, and cerebellar changes.

Diagnosis

Urine examination for metachorochromatic granules is a useful preliminary test. Thin layer of urinary sediment demonstrates marked increase in sulfatide levels. Nerve conduction studies demonstrate demyelnation of motor and sensory nerves. The protein content of CSF is elevated up to 150–300 mg/dL. The MRI reveals symmetrical confluent areas of T2 hyperintensity in periventricular white matter with posterior predominance and initial sparing of subcortical U-fibers **(Fig. 7)**. The *tigroid* and *leopard skin* patterns of demyelination, which suggest sparing of the perivascular white matter, can be seen in the periventricular white matter and centrum semiovale. The corpus callosum, internal capsule, and corticospinal tracts are also frequently involved.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

Megalencephalic leukoencephalopathy with subcortical cyst (MLC) was first described by van der Knaap in 1995. Molecular genetic testing has demonstrated mutations in *MLC 1* gene, which is located at chromosome *22qtel*. The inheritance of this disorder is autosomal recessive. It is a disorder, which is remarkable for its relatively mild neurological signs and symptoms in the setting of a very abnormal imaging study. It is characterized by delayed milestones, macrocephaly, a slow neurological deterioration with dysarthria and ataxia. Seizures, unusual in leukodystrophies are commonly reported. In India, this condition has been predominantly reported from the Agarwal community. MRI is diagnostic. It demonstrates diffusely hyperintense white matter (T2, FLAIR) of subcortical regions. The central white matter is spared; especially corpus callosum and occipital lobes. Subcortical cysts best appreciated on the FLAIR MRI sequences are seen in temporal and frontal lobes.

X-linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy is characterized by two distinct phenotypes: adrenomyeloneuropathy and cerebral demyelinating form of adrenoleukodystrophy. Both result from the mutation of the *ABCD1* gene. The cerebral demyelinating form of adrenoleukodystrophy is the most severe manifestation of this disorder. The onset is during school age or later in adulthood. Prominent clinical features include emotional liability, hyperactive behavior, school failure, visual failure, accompanied by lower limb spasticity, gait problems, and auditory impairment. Rapid dementia and seizures often occur. This results in a vegetative state within 2–4 years, and to death at varying intervals thereafter. Adults and children can have adrenal insufficiency that can precede the onset of neurological symptoms. The MRI findings are generally characteristic showing initial lesions in splenium of the corpus callosum and then the white matter of the parieto-occipital lobes **(Figs 4A and B)**.

GRAY MATTER DISORDERS

Certain disorders resulting in gray matter degeneration with marked systemic manifestations have been already discussed in Section 3 (Mucopolysaccharidosis, Gaucher's disease, Niemann-Pick Disease, Gangliosidoses) and Section 21 (Rett syndrome). Ataxia telangiectasia is already described in an earlier chapter in this Section. Others are detailed below:

Menkes Disease

Menkes disease is an X-linked recessive disorder of copper transport caused by diverse mutations in a copper transporting ATPase, ATP7A. Menkes disease typically presents in boys in infancy with loss of previously attained developmental milestones, hypotonia, seizures and failure to thrive. Skin and hair changes are characteristic. The scalp hair is classically short, sparse, light colored, coarse, and twisted. Light microscopy will illustrate the pathognomonic *pili torti* (180° twisting of the hair shaft) and often other abnormalities **(Figs 9A and B)**. The hair tends to be lightly pigmented but in some cases they can be normally pigmented as well. Tooth eruption is delayed. The skin often appears loose and redundant. Neurologically, severe hypotonia and poor head control are nearly always evident. Muscle stretch reflexes are often hyperactive. Seizures including infantile spasms are common and often refractory to treatment. Subdural hematomas are common **(Figs 9A and B)**. Pelvic ultrasonography reveals diverticula of the urinary bladder in nearly all children. Radiographs often disclose abnormalities of bone formation in the skull (wormian bones), long bones (metaphyseal spurring) and ribs (anterior flaring, multiple fractures). This disease should be considered as a differential diagnosis in boy with suspected battered baby syndrome. This is a severe neurological disease and in those with classical disease death usually occurs by 3 years of age.

Tay-Sachs Disease

Tay-Sachs disease is caused autosomal recessive disease caused by hexosaminidase-A deficiency. Tay-Sachs disease presents in early infancy as hypotonia and delayed milestones, associated with progressive macrocephaly, an exaggerated startle response, and cherry-red spots at the macula. Cherry red spots are seen in around 90% of the affected babies. Importantly there are no organomegaly or bone changes. This is a severe neurodegenerative condition with most children dying in early childhood. Late onset forms are less common and progress more slowly. They present with progressive ataxia, psychosis, or progressive muscular atrophy. Cognitive impairment and deterioration is also common.

Neuronal Ceroid Lipofuscinosis

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders. These disorders are characterized by progressive intellectual and motor deterioration, visual failure and seizures. *As a rule these group of disorders do not result in organomegaly, bone changes, or any coarsening of facial features.* Clinical phenotypes have been characterized traditionally according to the age of onset and order of appearance of clinical features into infantile, late-infantile, juvenile, adult, forms. However, there is considerable genetic and phenotypic heterogeneity. The same mutation can cause disease phenotype that is infantile onset and juvenile onset. Though the prevalence of various forms varies from region to region, the most prevalent NCLs are classic juvenile (CLN3 disease) and classic late infantile (CLN2 disease).

In the *classic late infantile* (CLN2) form, the first symptoms typically appear between age 2 years and 4 years, usually starting with seizures (myoclonic, generalized), followed by regression of developmental milestones, ataxia, and pyramidal signs. Visual impairment typically appears at age four to six years and rapidly progresses. Death usually occurs before teenage.

In the *classic juvenile* (CLN3 disease) form the onset is usually between ages four years and ten years. Rapidly progressing visual loss resulting in severe visual impairment within one to two years is often the first clinical sign. Many a time the children first report to an ophthalmologist for visual failure. Epilepsy with generalized tonic-clonic seizures and/or complex-partial seizures typically appears around age ten years. The loss of cognitive functions and intelligence occurs late and is slower in progression. The course may be variable and life expectancy ranges from the late teens to the forth decade.

Leigh Syndrome

Leigh syndrome is a group of severe neurodegenerative disease. The onset of Leigh syndrome typically occurs in infancy or early childhood. It typically manifests by rapid deterioration. In most cases, children do not display any dysmorphic features. However, various nonspecific abnormalities like prominent forehead and large ears might be observed. The onset of Leigh syndrome is often triggered by acute infections. Initial signs may include developmental regression with loss of previously acquired milestones. Other features include hypotonia or spasticity, dystonia, seizures, ataxia, dysphagia, ptosis, and abnormal eye movements such as nystagmus or slow saccades, breathing irregularities such as apnea. Further symptoms are failure to thrive and feeding difficulties.

In many children, the onset of symptoms is followed by a rapid deterioration and often death in infancy. Hallmarks of the disease are symmetrical lesions in the basal ganglia or brainstem on MRI imaging findings consists of bilateral, symmetrical hyperintensities on T2-weighted images **(Figs 6A to C)**. The lesions are commonly found in the basal ganglia, or in variable areas within the brainstem. They can also appear within several other CNS regions, such as the cerebellum, the thalamus and the spinal cord.

Numerous causative mutations in mitochondrial and nuclear genes, encoding components of the oxidative phosphorylation system have been described in the past years. Moreover, dysfunctions in pyruvate dehydrogenase complex or coenzyme Q_{10} metabolism may be associated with Leigh syndrome. Till date, there is no cure for affected patients, and treatment options are mostly unsatisfactory.

Wilson Disease

Wilson disease (WD) is caused by mutations in the *ATP7B* gene. WD begins with a presymptomatic period during which there is accumulation of copper in the liver that will cause hepatitis and, without treatment, will progress to liver cirrhosis and development of extrahepatic symptoms. The first neurologic symptoms of WD are commonly changes in behavior, deterioration in school performance, change in handwriting, dysarthria, drooling, tremor, or dystonia. The neurologic manifestations can be distinguished into three main phenotypes:

Dystonic Syndrome

It manifests as choreoathetosis and dystonic posturing. The dystonia may start slowly, focally and initially only during performing an action but soon progresses to other parts of body to become generalized. The involvement of facial muscles results in a fixed sardonic smile. Dysarthria results in a change in voice quality and occurs early in the disease course.

Parkinsonian Syndrome

The patient presents with rigidity and bradykinesia. Voice change and lack of facial expression are also prominent. Gait is unsteady with small steps, reduced postural reflexes, festination, and freezing.

Tremor Type

This phenotype is characterized by postural and action tremor with high amplitude and low frequency. Its proximal component can be well observed when a patient's arms are outstretched, showing the *wing-beating tremor*. It is sometimes associated with cerebellar syndrome.

Other Extrahepatic Features

Kayser-Fleischer (KF) rings on the cornea are detected by slit-lamp examination in most children with neurological manifestations. Other eye findings include sunflower cataracts and oculomotor abnormalities. Other extrahepatic features include renal stones, renal tubular acidosis, hemolytic anemia, osteoarticular disorders, myocardial abnormalities and endocrine disturbances.

Pantothenate Kinase-associated Neurodegeneration

Previously called Hallervorden-Spatz disease, pantothenate kinase-associated neurodegeneration (PKAN) is a recessive autosomal disease caused by a mutation of the gene (20p13–p12.3) encoding pantothenate kinase 2 (PANK2), an essential mitochondrial enzyme involved in coenzyme A biosynthesis. PKAN classically begins with gait abnormalities, generally before the age of 6 years. Dystonic posturing is often prominent, it can be asymmetric. Others symptoms include dysarthria, extrapyramidal syndrome, cognitive deterioration, or a neuropsychiatric disorder. About two-thirds of patients have clinical or electroretinographic

evidence of retinopathy manifesting as retinitis pigmentosa. Some children may have an atypical presentation with later onset (teenage) and slower progression. Classic and atypical PKAN patients show the same findings on brain MRI. In globus pallidus, the *eye of the tiger* sign consists of bilateral areas of hyperintensity (corresponding to necrosis tissue) surrounded by a ring of hyposignal (high iron) on T2-weighted sequences **(Fig. 3)**.

MORE ON THIS TOPIC

Fenichel GM. Clinical Pediatric Neurology; A Signs and Symptoms Approach. 5th ed. Philadelphia: Elsevier; 2005.

Lyon G, Kolodny EH, Pastores GM. Neurology of Hereditary Metabolic Diseases in Children. 3rd ed. New York: McGraw-Hill; 2006.

Michelson DJ, Shu SK. Cognitive and Motor regression. In: Swaiman KF, Ashwal S, Ferriero DM. Pediatric Neurology. 4th ed. Philadelphia: Elsevier; 2006. pp. 821-44.

Neurologic syndrome. In: Clarke JTR. A Clinical Guide to Inherited Metabolic Diseases. 3rd ed. Cambridge: Cambridge University Press; 2006. pp. 28-89.

IN A NUTSHELL

1. A thorough clinical evaluation that includes a detailed history, family history, general physical, neurological and systemic evaluation forms an important starting point for evaluation of NDDs.
2. The investigations are planned to support and later confirm the diagnosis. Diagnostic testing can be undertaken as per clues obtained from history and examination, e.g., HIV testing, urine mucopolysaccharidosis, VLCFA, etc.
3. Treatable causes should be excluded first. Supportive therapy should be undertaken in all children to make the child's life comfortable, e.g., control seizures, spasticity, adequate nutrition and skin care, etc.
4. The ultimate goal of clinical evaluation and investigations is to offer preventive diagnosis for future children and possibly identify and treat pre or pauci symptomatic individuals in the family.

Chapter 42.27
Spinal Cord Disorders
Vykunta Raju KN

The diagnosis and treatment of pediatric spinal disorders differs significantly from that of adult spinal disorders. If we recognize and treat spinal cord disorders, permanent severe neurologic disability can be minimized. A wide variety of congenital, developmental, traumatic and neoplastic disorders may occur in children. Given the rapid growth that occurs in children, problems in the spine may become evident due to the development of scoliosis, pain, or neurological problems such as weakness or numbness. Unlike adult treatments, the surgical treatment of these disorders in children must take into account the expected growth and development of the spine.

EPIDEMIOLOGY

Spinal cord injuries (SCIs) and myelomeningocele are two most common pediatric spinal cord disorders. Neural tube defects are the most common congenital malformation and their incidence in North India is as high as 3.9–9/1000 live births and may be higher in still births. Neural tube defects are discussed in the chapter on neural tube defects.

ANATOMY OF SPINAL CORD

The spinal cord lies within the vertebral canal. It extends from the foramen magnum, where it joins medulla to the level of the first or second lumbar vertebra. Disparity exists between vertebral and segmental cord level with age, at birth it lies at L2 vertebrae. It is oval in shape, and has two enlargements in the cervical and lumbar regions corresponding to the outflow of nerves to the limbs. At its lower end, it terminates in the conus medullaris, from the end of which a delicate filament, the filum terminale, continues downwards to the posterior surface of the coccyx. The spinal cord is regarded as being organized into segments, one corresponding to each pair of spinal nerves. There are 8 cervical, 12 dorsal or thoracic, 5 lumbar, 5 sacral segments, and 1 coccygeal. Since spinal cord ends at the first or second lumbar vertebra, all the spinal nerves below the first lumbar descend to their respective foramina in a bundle of nerves known as the cauda equina.

The spinal cord, like the brain, is surrounded by three meninges, pia mater, arachnoid and dura mater. On the transverse section, the cord substance is seen to be divided into the central gray and peripheral white matter. The gray matter is composed of ganglion cells and nerve fibers, and the white matter of fibers and their myelin sheaths. The gray matter forms an H-shaped mass, composed of an anterior and posterior horn on each side, united by the gray commissure, in the middle of which lies the central canal. The anterior horns contain ganglion cells, the axons of which enter the anterior roots and form the lower motor neurons. The white matter, consisting of longitudinal bundles of nerve fibers, is regarded as being divided into three columns. The bony spine, provide protection for the spinal cord from excessive movement. Cervical region of spinal cord is more prone for injury because of it is most mobile part.

BLOOD SUPPLY

The spinal cord is richly supplied with blood. There are two posterior spinal arteries, each derived from the corresponding vertebral or posteroinferior cerebellar artery. The single anterior spinal artery is formed by the union of a branch from each vertebral artery. The spinal arteries are reinforced by segmental arteries. The two most important of these are one at C6, and one, the great anterior radicular artery of Adamkiewicz, which usually enters the spinal cord between the T5 and T8 segments. Branches from anterior spinal artery supply the anterior columns and most of the lateral columns. Branches from posterior spinal artery supply the entire posterior columns and the remainder of the lateral columns.

CLINICAL FEATURES OF SPINAL CORD LESIONS

This section discusses the general features of spinal cord lesions and specific findings according to the segmental level of the cord lesion. The signs and symptoms of spinal cord disorders are dependent on the level, longitudinal and transverse extent, and pathological nature of the underlying cause. **Table 1** shows clinical features of spinal cord dysfunction by segmental level location of lesions. **Table 2** shows central cord syndromes, where segments below may be spared. **Table 3** shows how to differentiate intramedullary from extramedullary lesions.

Sensory, motor, and sphincter manifestations are each common and classical features of spinal cord disease, although partial may involve only one or two of these functions. Symptoms include weakness below the level of the lesion, with difficulties

Table 1 Effects of spinal cord dysfunction by segmental level

Location of Lesion*	Possible Effects
At or above C5	Respiratory paralysis Quadriplegia
Between C5 and C6	Paralysis of legs, wrists, and hands Weakness of shoulder abduction and elbow flexion Loss of biceps jerk reflex Loss of brachioradialis deep tendon reflex
Between C6 and C7	Paralysis of legs, wrists, and hands, but shoulder movement and elbow flexion usually possible
Between C7 and C8	Loss of triceps jerk reflex Paralysis of legs and hands
At C8–T1	Horner syndrome (constricted pupil, ptosis, facial anhidrosis) Paralysis of legs
Between T1 and conus medullaris	Paralysis of legs

*Abbreviations refer to vertebrae; the cord is shorter than the spine, so that moving down the spine, cord segments and vertebral levels are increasingly out of alignment. At all levels of cord injury, deep tendon reflexes are altered (initially decreased and later becoming brisk) below the level of the lesion, bowel and bladder control is lost, and sensation is lost below the level of injury.

Table 2 Spinal cord syndromes, their causes, and clinical presentation

Syndrome	Cause	Symptoms and signs
Anterior cord syndrome	Lesions disproportionately affecting the anterior spinal cord, commonly due to infarction (e.g., Caused by occlusion of the anterior spinal artery)	Malfunction of all the tracts except posterior columns, thus sparing position and vibration sensation
Brown-Sequard syndrome	Unilateral spinal cord lesions, typically due to penetrating trauma	Ipsilateral paresis Ipsilateral loss of touch, position, and vibratory sensation Contralateral loss of pain and temperature sensation*
Central cord syndrome affecting the cervical spinal cord	Lesions affecting the center of the cervical spinal cord, mainly central gray matter (including spinothalamic tracts, which cross), commonly due to trauma, syrinx, or tumors in the central spinal cord	Paresis tending to be more severe in the upper extremities than in the lower extremities and sacral regions Loss of pain and temperature sensation in a cape-like distribution over the upper neck, shoulders, and upper trunk, with light touch, position, and vibratory sensation relatively preserved (dissociated sensory loss)
Conus medullaris syndrome	Lesions around L1	Distal leg paresis Perianal and perineal loss of sensation (saddle anesthesia) Urinary retention, frequency, or incontinence Fecal incontinence Hypotonic anal sphincter Abnormal bulbocavernosus and anal wink reflexes
Transverse myelopathy	Lesions affecting all or most tracts of the spinal cord at ≥ 1 segmental level	Deficits in all functions mediated by the spinal cord (because all tracts are affected to some degree)

*Occasionally, only part of one side of the spinal cord malfunctions (partial Brown-Sequard syndrome).

Table 3 Clinical guidelines to differentiate intramedullary and extramedullary tumors

Symptoms/signs	Intramedullary tumors	Extramedullary tumors
Radicular pain	Unusual	Common, may occur early
Vertebral pain	Unusual	Common
Funicular pain	Common	Less common
Upper motor neuron signs	Yes, late	Yes, early
Lower motor signs	Prominent and diffuse	Unusual, if present, segmental distribution
Paresthesia's progression	Descending progression	Ascending
Sphincter abnormalities	Early with caudal lesion (conus cauda equina)	Late
Trophic changes	Common	Unusual

in walking or upper limb function. Sensory symptoms include numbness, tingling, pins and needles, dermal hypersensitivity, burning sensation, altered temperature sensation, and tight band like feelings below the level of lesions. Loss of all voluntary movements and sensation will occur at the level of the lesions, especially when there is spinal cord compression from extrinsic disease involving the vertebral column. The most common sphincter disturbances resulting from spinal cord disease are urgency, frequency, and urge incontinence; less commonly hesitancy or retention occur, except in acute transverse lesions where retention is the rule. Constipation and fecal incontinence occurs, though less often. Other autonomic changes may also be seen, e.g., excessive sweating or vasomotor disturbances below the site of lesion, or Horner syndrome with lesion in the cervical cord.

The clinical signs may be divided into those occurring at the level of the lesion and those due to interruption of long tracts. At the level of a lesion, there may be lower motor neuron signs, with focal muscle wasting, fasciculations, and hypo-or areflexia due to involvement of anterior horn cells. Radicular pain or dermatomal sensory loss may result from damage to sensory roots. The interruption of long tracts will result in upper motor sings below the level of the lesion, with pyramidal pattern of weakness, spasticity, and deep tendon hyper-reflexia with absent abdominal reflexes and extensor plantar responses. Acute severe cord lesions produce a flaccid paraplegia with temporary phase of hypotonia and areflexia before appearance of more characteristic UMN signs.

A complete cord syndrome will result in loss of all sensory modalities below the level of the lesion. Partial syndromes will produce variable findings—posterior column involvement leads to loss of joint position sense, vibration, and two point discrimination, with a positive Romberg's sign and an ataxic gait. Contralateral loss of pain and temperature sensation occurs with lesions involving spinothalamic pathways.

Cauda equina syndrome due to damage to nerve roots at the caudal end of the cord mimics conus medullaris syndrome. It causes distal leg paresis and sensory loss in and around the perineum and anus (saddle anesthesia), as well as bladder, bowel, and pudendal dysfunction. Muscle tone and deep tendon reflexes are decreased in the legs.

DIAGNOSIS

Segmental level neurological deficit suggests spinal cord disorder. Unilateral segmental deficits may result from nerve root or peripheral nerve disorders. Location of a spinal cord lesion can be determined by level and pattern of spinal cord dysfunction. MRI of spine is very useful imaging test for spinal cord lesions. It shows

spinal cord parenchyma, soft tissue lesions, and bone lesions. Plain X-rays are helpful for detection of bone lesions. Myelography is used less often.

MANAGEMENT

The principles of management in children with spinal cord disorders are different from adults. It must be developmentally based and one should consider dynamic changes that occur as a consequence of growth and development.

DISORDERS OF SPINAL CORD

Syringomyelia

It is a fluid-filled cavity within the spinal cord. Some of the predisposing factors are craniocervical junction abnormalities, previous spine injury, and spinal cord tumors. Usually, it results from partial obstruction to CSF flow. At least fifty percent of syringomyelia occurs in children with congenital anomalies (e.g., Chiari malformation, myelomeningocele). It usually begins in the cervical region but extend downward along the entire length of the spinal cord.

Symptoms and Signs

Syringomyelia usually produces central cord syndrome (Table 2). Initially pain and temperature sensory loss occurs. It is usually in a cape-like distribution over the shoulders, arms, and back. It may cause painless burn or cut. It produces weakness, atrophy, fasciculations and hyporeflexia in the upper limbs. Position, vibration sensation and light touch are not affected. Later spasticity in the lower limbs develops. Findings may be asymmetric. MRI of spine with contrast helps in diagnosing syringomyelia and associated anomalies.

Management

Surgical decompression of the foramen magnum and cervical cord is indicated, but it will not reverse severe neurodeficits. Underlying problems are corrected when possible (e.g., anomalies, tumor, etc.)

Craniocervical Junction Abnormalities

Craniocervical junction abnormalities are abnormalities of the occipital bone, foramen magnum, or first two cervical vertebrae. These disorders ranges from asymptomatic problems to devastating neurological problems. The clinical manifestation reflects in the anatomical structures in this region, brainstem, cerebellum, cranial nerves, spinal cord and vertebrae. **Box 1** shows craniovertebral abnormalities and their clinical consequences.

BOX 1 Craniocervical abnormalities and their clinical consequences
• *Fusion of the atlas (C1) and occipital bone:* Spinal cord compression if the anteroposterior diameter of the foramen magnum behind the odontoid process is < 19 mm
• *Basilar invagination (upward bulging of the occipital condyles):* A short neck and compression that can affect the cerebellum, brainstem, lower cranial nerves, and spinal cord
• *Atlantoaxial subluxation or dislocation (displacement of the atlas anteriorly in relation to the axis):* Acute or chronic spinal cord compression
• *Klippel-Feil malformation (fusion of cervical vertebrae):* Deformity and limited motion of the neck but usually no neurologic consequences
• *Platybasia (flattening of the skull-base so that the angle formed by the intersection of the clival and anterior fossa planes is > 135°), seen on lateral skull imaging:* No symptoms or cerebellar or spinal cord deficits or normal-pressure hydrocephalus.

Etiology

Os odontoideum is abnormal bone that replaces odontoid process (**Fig. 1**). Congenital fusion of the atlas and occipital bone is atlas assimilation. *Klippel-Feil anomaly* may be associated with atlanto-occipital anomalies. *Platybasia* may be seen in Chiari malformation. *Achondroplasia* can cause narrow foramen magnum and it may compress the spinal cord. *Atlantoaxial subluxation* or dislocation can be seen in Down syndrome and Morquio syndrome. Although the exact mechanisms of this condition are uncertain, the problem may be related to weakness, laxity of the ligaments and/or abnormalities of bone development. These problems are usually diagnosed between the ages of 6 and 12 years.

Clinical Features

Clinical manifestation can occur spontaneously or after minor neck injury. Presentation depends on degree of compression and structures affected. Common manifestations are headache, neck pain and features of spinal cord compression. Short neck, torticollis, restriction of movements can be seen in some abnormalities (e.g., Klippel-Feil malformation, platybasia, basilar invagination). Sometimes brainstem, cranial nerve and cerebellar deficits can be seen. Vertebrobasilar ischemia can cause intermittent syncope, drop attacks, vertigo, weakness, visual disturbance or altered sensorium.

Diagnosis

MRI of spine detects neural lesions and soft tissue lesions. CT scan shows bone structures and may be done more easily during emergency. Plain X-rays and myelography are sometimes useful.

Treatment

Reduction of craniocervical junction is indicated if lesions are causing neural compression. Head and neck should be immobilized. If reduction is not successful, surgical decompression is indicated. Posterior fixation is indicated if instability persists after decompression.

Tuberculous Spinal Osteitis

Tuberculous spinal infection is still common in less developed regions of the world. The infective process generally begins in the vertebral body and spreads to adjacent bodies, leading their collapse and an angular deformity of the spine (**Figs 2A to C**). It is rare for the deformity as such to be a major factor in compressing

Figure 1 Atlantoaxial dislocation with presence of os odontoideum. Dens is retroflexed and seen causing spinal canal stenosis and cord compression
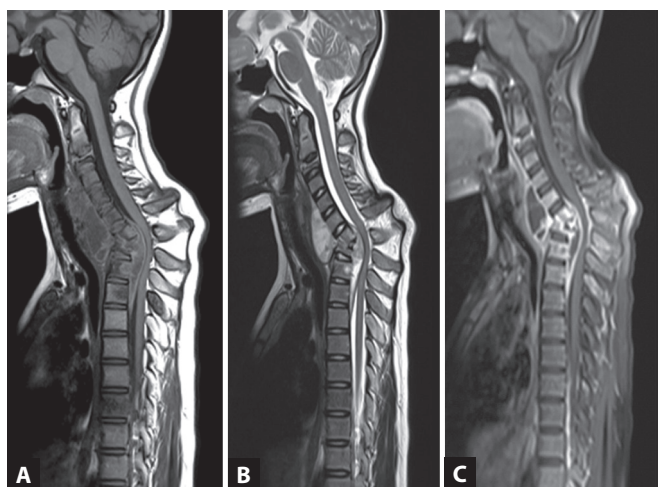
Figures 2A to C 14-year-old female presented with history of fever, neck pain, and weakness of all four limbs since 15 days. (A) T1 sagittal; (B) T2 sagittal; (C) Postcontrast T1. There is anterior wedge collapse with destruction of the C7 and D1 vertebrae and the intervertebral disc, causing a kyphotic deformity. A large heterogeneous mass is seen in the adjacent anterior epidural space (C7–D4 levels) and the pre- and paravertebral regions (C4–D2 levels). The epidural lesion is seen to severely compromise the spinal canal (diameter of up to 7 mm). The lesion is hyperintense on T2WI and hypointense on T1WI. Evidence of diffusion restriction seen. On the postcontrast scan, the lesion shows peripheral enhancement. Features are suggestive of tuberculosis of spine. There is vertebra plana of the C3 vertebra with an adjacent enhancing mass on left side

the cord, which is more often affected by an extradural tuberculous abscess or tuberculous meningomyelitis. In addition to actual cord compression, which may, however, be absent, interference with the vascular supply of subjacent segments, either by compression of radicular arteries or by endarteritis, is an important factor in producing paraplegia. These conditions probably explain the good outcome that can be achieved by conservative treatment using antituberculous chemotherapy rather than surgical decompression, even in severe cases.

Viral Myelitis

Viral causes of myelitis include poliomyelitis, coxsackie viruses, herpes zoster, herpes simplex, HIV, Epstein-Barr virus, cytomegalovirus (CMV), and HTLV-1. Although number of viruses causes an acute infective myelitis, they may also be associated with a postinfectious myelitis, which is likely not to be the result of viral infection but rather to an immune-mediated response triggered by the viral antigens.

Poliomyelitis and coxsackie viruses produce an acute inflammatory meningomyelitis with cord involvement predominantly affecting the anterior horn cells, leading to patchy, multifocal or sometimes extensive muscle weakness and wasting, with corresponding reflex loss but no sensory abnormality. Varicella zoster usually produces a sensory dermatomal deficit, often with marked pain, due to predominant involvement of the dorsal root ganglion. The associated dermatomal vesicular rash will normally establish the diagnosis.

A transverse myelitis due to viral infections such as those above, although much rarer, may be indistinguishable from a post-infectious transverse myelitis. Such infections are more likely to occur in immunocompromised states, including those with HIV infection. The diagnosis is confirmed by the isolation of portions of viral antigen from the CSF by PCR.

Spinal Cord Injury

Spinal injuries are common at the C1–C2 level in children of 0–3 years old. This is probably due to higher fulcrum of motion in younger children, and weakness of C2 vertebra. Common causes are motor vehicle accidents, falls, recreational or sports activities (e.g., diving accidents and football injuries), and penetration injuries of spine (e.g., knife, gunshot). Violence is common in the age group of 16–20 years. Traumatic birth injury is decreasing. The death due to spinal cord trauma is more common in children compared to adults. **Box 2** shows predisposing conditions to cervical spine injuries.

Major ways of spinal trauma causing spinal cord injury are: forward flexion, lateral flexion, rotation, axial compression, and hyperextension. These forces can result in vertebral distraction, dislocation, fracture, and disc herniation. Bone disruption (fracture or displacement) is the most common cause of spinal cord injury. Spinal cord injury without radiographic abnormality (SCIWORA) is common in children where ligamentous injury causes spinal injury without bone disruption.

Forward flexion injury is seen in children wearing ill-fitting adult types of lap-sash belts (cervical seat-belt syndrome). Axial compression occurs in diving accidents, falls, and sports injuries. Severe hyperextension is seen in the head-shaking injury of child abuse, after neck hyperextension in football games and in infants with C1 to C2 instability.

X-ray of spine may be useful to detect osseous disruption; however it can be normal in 50% of children. CT spine detects subtle spinal fractures. MRI of spine recently replaced CT and myelography as imaging of choice in spinal cord disorders. Stabilization of spine to prevent further injury is important. Intravenous methylprednisolone, bolus of 30 mg/kg followed by infusion at 5.4 mg/kg/hour over next 23 hours can be considered. The benefit is modest at best, and one needs to weigh the risk of potentially serious complications of high dose steroids.

SPINAL CORD TUMORS

Neoplasms of the spinal cord are less common than those found intracranially. The ratio of intracranial/intraspinal neoplasms in children depends on the histology of the tumor. The ratio varies from 20:1 to 5:1. Spinal cord tumors are most commonly found in the thoracic spinal cord followed by location in the cervical, thoracolumbar, and lumbosacral areas. Thus, the divisions having the largest number of segments are areas associated with the highest incidence of tumor.

Types of Tumor

Traditionally, tumors of the spinal canal are divided into extramedullary and intramedullary masses **(Table 4)**.

Extramedullary Tumors

Extramedullary masses erode the bony vertebral column, present asymmetrically, and involve those sensory and motor tracts placed laterally within the substance of the spinal cord parenchyma. Dumbbell lesions, consisting of neurofibromas presenting both inside and outside the neuroforamina, are occasionally encountered.

BOX 2   Predisposing factors for cervical spinal cord injury

- Down syndrome (15% have atlantoaxial instability)
- Klippel-Feil syndrome
- Morquio syndrome
- Larsen syndrome
- Achondroplasia
- Previous spine surgery.

Table 4 Tumors of the spinal cord

Intramedullary	Extramedullary
Astrocytomas • Cystic • Noncystic Ependymomas • Myxopapillary • Well-differentiated Oligodendroglimas	Neurofibromas Dysembryoplastic • Dermoids • Epidermoids • Teratomas • Lipomas Meningiomas Arachnoid cysts Metastatic • Neuroblastoma • Sarcoma • Lymphoma

Reticulum cell sarcomas, lymphomas, neuroblastomas, and other sarcomatous lesions usually present in the context of neoplasms found elsewhere in the body. In the spinal cord, they occur epidurally and present as compressive lesions. Dysembryoplastic lesions are observed in the younger child. The findings of teeth, bones, or calcification on X-ray film suggest a dermoid. These findings may be associated with a sinus tract leading from the surface and extending intraspinally. As with dermoids, tumors usually occur in the lumbosacral midline region, although they may occur anywhere in the spinal column, and may be associated with spina bifida, sacral dimple, port-wine nevus, or excessive clumps of coarse hair. At surgery, the tract extends to the conus. Nerve roots of the cauda equina are often enmeshed in the fatty tumor with varying degrees of neurologic abnormalities. The serpiginous nature of these fatty tumors may make surgery difficult. Despite this problem, with or without surgery, patients often remain relatively stable with little progression of symptoms.

Intramedullary Tumors

Thirty five percent of the pediatric intraspinal tumors are intramedullary. The most intramedullary tumors in children are either astrocytomas or ependymomas. Astrocytomas present as a mass extending over multiple segments of the cord or the entire length of the spinal cord. They may be partially cystic. Because these tumors expand and compress normal tissue, they are more likely to produce slowly progressive signs rather than sudden interruption of neurologic function. Astrocytomas of the spinal cord have hamartomatous features consequently their natural history may be quite prolonged. Gross total resection is the treatment of choice, in the presence of dissemination radiation can provide long-term survivals. In contrast, high grade astrocytomas of the spinal cord have a poor prognosis with median survival of 12 months.

Ependymomas are less common than astrocytomas. These are classified into two types: well differentiated cellular or well-differentiated myxopapillary tumors. Treatment consists of laminectomy with decompression and attempt at complete removal. Complete removal is the treatment of choice, resulting in cure. Radiation can be considered if tumor not resected completely. In general, the prognosis for ependymomas of the spinal cord is better than for astrocytoma, with 5-year survival rates of 72–100%.

Clinical Characteristics

Signs and symptoms of spinal cord neoplasms can be insidious and misleading. History is often vague, and early in the course of the disease there may be a paucity of clinical signs. Common complaints are extremity weakness, abnormalities of gait, or pain in the extremities, back, or even periumbilical region. Unfortunately, consideration of a spinal cord mass may not enter the differential diagnosis until there is considerable progression or a spinal cord sensory level becomes obvious. In young children, because enuresis is common, a history of changing patterns of continence may not be elicited. In the very young, who are not bowel or bladder trained, sphincter abnormalities may be over-looked. A clue to the presence of neurogenic bladder is incontinence of urine associated with crying or straining at stool. Loss of rectal tone is a common finding in patients with spinal cord tumors.

Changes in posture, nonspecific complaints of back pain, or even unexplained abdominal pain may by associated with disease of the spinal cord. Pain is more often dull aching, burning, and diffuse, rather than sharp. Sharp pain is uncommon. Classic signs of a sensory level with or without a Brown-Sequard syndrome are rarely encountered.

Any pain accentuated by either Valsalva maneuvers, such as sneezing, coughing, or straining at stool, or by straight leg rising should be evaluated. These maneuvers, by stretching the meninges, may cause root irritation in a patient with compressive disease of the spinal canal.

Subtle physical findings may be mild scoliosis, discrepancy in foot or leg length, or vasomotor changes in the lower extremities. Findings are hyper-reflexia, clonus, and Babinski responses suggest disease of the corticospinal tracts. Proprioceptive, vibratory loss, or a sensory level, no matter how subtle, should raise suspicion of intraspinal pathology.

Diagnostic Studies

X-ray spine—an increase in the interpedicular distance may suggest a long standing intramedullary process. Destructive changes of bone are more frequently associated with metastatic disease. Distortion or widening of the neuroforamina may be observed with extramedullary tumors, such as neurofibromas or metastatic disease to the spinal canal. With slowly growing intraspinal tumors, the changing forces of an asymmetrical spinal lesion may alter vertebral growth in such a manner as to cause scoliosis. Bony abnormalities may be associated with a paravertebral soft tissue mass.

Diagnosis is confirmed by neuroimaging. MRI can visualize the entire length of the cord in the sagittal diameter. By this method, intramedullary masses can be readily separated from extramedullary lesions. Further, unlike myelography, MRI readily identifies intramedullary cysts. **Figures 3A to D** shows osteochondroma at C2 vertebra causing spinal cord compression.
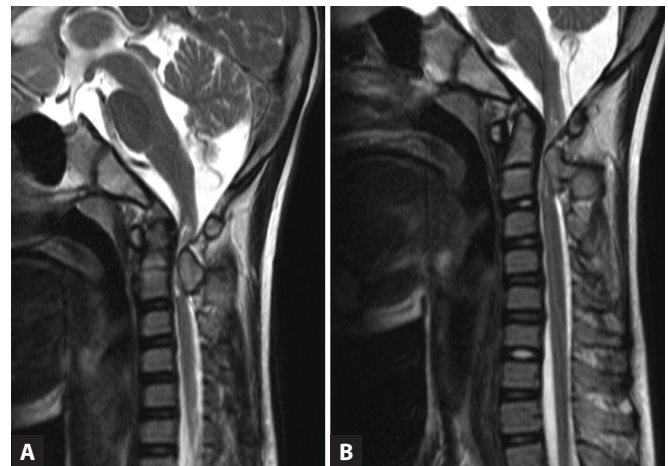
Figures 3A and B Osteochondroma at C2 vertebra. 11-year-old girl presented with neck pain and quadriparesis. Mid sagittal and parasagittal T2 MR images of the cervical spine demonstrate osteochondroma arising from the right C2 lamina causing severe spinal canal narrowing with compressing the spinal cord and spinal cord signal changes
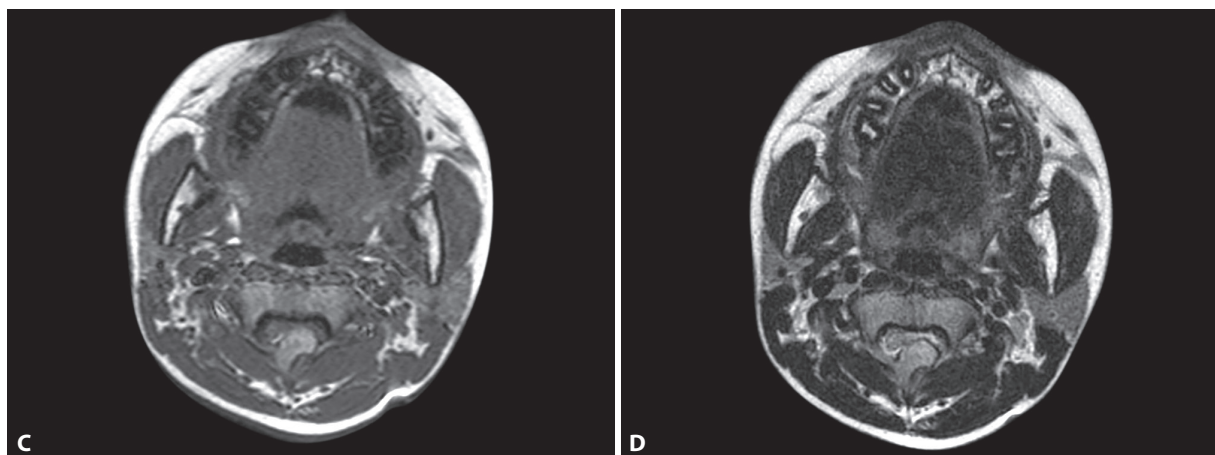
Figures 3C and D Axial T1 and T2 MR images of the cervical spine demonstrate osteochondroma arising from the right C2 lamina causing severe spinal canal narrowing with compressing the spinal cord and spinal cord signal changes

Management

Surgery

In all cases, regardless of etiology and extent of defects, surgical decompression is recommended. The spinal cord is resilient. In general, recovery depends on the length and duration of symptoms. Any evidence of compression of long tract motor or sensory function through the spinal cord limits hope for recovery.

Adjuvant Management

Radiation is recommended for subtotally resected spinal cord tumors: however, even this approach is not without controversy. Many suggest radiation of all subtotally resected intramedullary tumors, regardless of histology. Recommended radiation doses to the lesion range between 2500 cGy and 5000 cGy in 180–200 cGy fractions with a margin of 2–3 cm.

Chemotherapy

There is lack of data on use of chemotherapy in low grade astrocytomas of the spinal cord. Most commonly, varying combinations of carboplatin and vincristine have been used.

Complications

The main complications after treatment of spinal cord tumors are orthopedic. Radiation-associated arachnoiditis or myelopathy also contributes to orthopedic abnormalities. Non-neurologic complications are kyphoscoliosis and, after radiation, limited growth of the vertebral column. Neurologic complication after surgical treatment may be flaccid or spastic paraplegia or quadriplegia and bowel or bladder incontinence. Decubitus ulcers, pathologic fractures, and dislocated hips may occur because of loss of trophic neurologic input. Although treatment may be curative, morbidity can be significant. Skilled and continuous rehabilitative care is necessary to improve the quality of life.

Prognosis

Prognosis for spinal cord tumors is much better than that for the child with an intracranial tumor. Surgical intervention may delay

the growth and progression of these tumors. In the more aggressive tumors surgery coupled with judicious use of radiotherapy has been associated with long-term survival or cure. Unfortunately, morbidity is quite significant. The insidious nature of spinal cord tumors, their relative rarity, and their lack of clinical specificity continue to challenge the most astute neurologic clinicians.

IN A NUTSHELL

1. Rapid evacuation and treatment prevents permanent severe neurologic disability.
2. MRI is the imaging of choice for spinal cord disorders.
3. Spinal dermoid can cause recurrent meningitis.
4. Good outcome can be achieved by conservative treatment using antituberculous chemotherapy for tuberculosis of spine.
5. Spinal cord injury without radiographic abnormality (SCIWORA) is ligamentous injury causing spinal cord injury without bone disruption is common in children.
6. The surgical treatment of spinal disorders in children must take into account the expected growth and development of the spine.

MORE ON THIS TOPIC

Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol. 2013;12:799-810.

Garton HJ, Hammer MR: Detection of pediatric cervical spine injury. Neurosurgery. 2008;62:700-8.

Kalra V. Practical Pediatric Neurology. 2nd ed, New Delhi: Arya Publications; 2008.

Menezes AH. Cranivertebral junction database analysis: incidence, classification, presentation, and treatment algorithms. Childs Nerv Syst. 2008;24: 1101-8.

Brazis PW. Localization in Clinical Neurology. 6th ed. Wolters Kluwer Lippincott Williams and Wilkins; 2011.

Polk-Williams A, Carr BG, Blinman TA. Cervical spine injury in young children: a National Trauma Data Bank review. J Pediatr Surg.2008;43:1718-21.

Chapter 42.28
Pseudotumor Cerebri
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Pseudotumor cerebri (also known as benign intracranial hypertension or primary idiopathic intracranial hypertension) is a clinical syndrome with raised intracranial pressure in the absence of space-occupying lesion or apparent obstruction to the CSF pathways. This increased intracranial pressure is marked at more than 200 mm in infants and more than 250 mm in children. Papilledema is universally present in older children whose fontanel is closed. To some extent it is a diagnosis of exclusion, dependent on excluding identifiable causes of raised intracranial pressure. It can be *primary* or *secondary*. The main causes of pseudotumor cerebri are listed in **Table 1**.

CLINICAL FEATURES AND DIAGNOSIS

Headache is the most common feature and often the sole presenting complaint. This is made worse by maneuvers that raise the intracranial pressure, such as coughing and bending. Transient visual impairment and diplopia (secondary to VI cranial nerve palsy) may also be seen. Most patients though are alert and lack constitutional symptoms. Infants may manifest with irritability, the sunset sign, and a bulging anterior fontanel. Papilledema (occasionally with hemorrhages) or at least some degree of blurring of the disc margins is the hallmark of the disease. Most often the papilledema is bilateral, although it can be asymmetric or unilateral. An MRI with a venogram is useful to rule out dural venous sinus thrombosis. The investigations which need to be performed in a patient with pseudotumor cerebri are detailed in **Box 1**. Visual loss is the main concern and complication (questioning the term *benign* attached to this variant of raised intracranial tension). Sequential perimetry and assessments of visual acuity are advised. Diagnostic criteria for pseudotumor cerebri are shown in **Box 2**.

TREATMENT

Treatment includes elimination of contributory factors like weight, drugs and diet and treatment of the underlying cause. The initial lumbar puncture is both diagnostic and can be therapeutic to release the raised intracranial pressure. Serial lumbar punctures are then done every 5–7 days, with drainage of 20–25 mL of CSF on each tap to lower the closing pressure below 200 or 250 mm Hg in infants and children, respectively. Acetazolamide (10–30 mg/kg/day in two divided doses) or diuretics like furosemide (1 mg/kg/day in two divided doses) decrease the formation of CSF and are used in children with unimpaired visual function. Topiramate and steroids are other pharmacological therapies found to be useful.

The main indications for surgical intervention are deterioration in vision and severe incapacitating headaches despite aggressive medical management. An optic nerve sheath fenestration and CSF diversion (usually, lumboperitoneal shunting) are modalities out of which the former one is usually preferred.

Optic nerve sheath fenestration involves cutting slits or rectangular patches in the dura surrounding the optic nerve immediately behind the globe allowing direct drainage of CSF into the orbital fat, where it is absorbed into the venous circulation. The fenestration besides lowering the optic nerve edema and restoring visual function also acts as a safety valve and keeps the pressure from being transmitted to the optic nerve. However, besides complications of diplopia and optic nerve injury in one-third of cases secondary visual decline may occur in a few years necessitating a repeat surgery or alternative treatment.

Table 1 Etiology and classification of pseudotumor cerebri

Primary pseudotumor cerebri No recognized cause (Idiopathic pseudotumor cerebri)		
Secondary pseudotumor cerebri		
Drugs	*Systemic disorders*	*Metabolic disorders*

• Use of corticosteroids or corticosteroid withdrawal
• Hypervitaminosis A
• Tetracyclines or minocycline
• Nalidixic acid
• Phenothiazines
• Sulfonamides
• Oral contraceptives
• Phenytoin
• Cyclosporine
• Cytarabine
	I. Secondary to neurological disorders
	  • Dural venous sinus thrombosis (associated with otitis media, mastoiditis, or head trauma)
	  • Altered CSF composition (meningitis)
	  • Arteriovenous malformation draining into a venous sinus (Dural arteriovenous fistula)
	  • Guillain-Barré syndrome
	
	II. Secondary to systemic disorders
	  • Hypovitaminosis A
	  • Systemic lupus erythematous
	  • Behçet disease
	  • Antiphospholipid syndrome
	  • Familial deficiency of antithrombin III
	  • Severe anemia (aplastic or iron deficiency, Wiskott-Aldrich syndrome)
	  • Nephrotic syndrome
	  • Leukemia
	  • Non-Hodgkin lymphoma
	  • Turner syndrome
	  • Crohn disease
		• Obesity
		• Refeeding of malnourished children
		• Menarche
		• Pregnancy
		• Hypoparathyroidism
		• Hyperparathyroidism
		• Hyperthyroidism
		• Thyroxine replacement
		• Hyperadrenalism
		• Addison disease
		• Vitamin D-dependent rickets
		• Hypophosphatasia

BOX 1 Investigations in a patient suspected with pseudotumor cerebri

- *Hematological investigations* for ruling out metabolic and systemic disorders:
  - Complete blood count and erythrocyte sedimentation rate
  - Autoimmune disorder profile (ANA profile, e.g., anti-dsDNA and anti-ssDNA)
  - Prothrombotic profile (e.g., Protein S, Protein C, homocysteine levels, antithrombin III, factor V Leiden variant, antiphospholipid/anticardiolipin antibodies, lupus anticoagulant, and platelet aggregation studies to name a few)
- *CSF examination* including the opening pressure which is vital for diagnosis along with routine glucose, cell count and protein examinations. However, it should always be kept in mind that brain imaging should be obtained before a lumbar puncture is performed
- *Neuroimaging*
  - Magnetic resonance imaging (MRI) of the brain with magnetic resonance venography (MRV) is preferred to enable one to exclude thrombosis of a major venous sinus.
  - Ultrasonography has been used to measure the diameter of the optic nerve sheath.
- *Optic nerve function* should be carefully monitored with an assessment of visual acuity, color vision, optic nerve head appearance, and perimetry.

BOX 2 Modified Dandy criteria for pseudotumor cerebri

1. Signs and symptoms of increased intracranial pressure
2. No localizing neurological signs except for unilateral or bilateral VI cranial nerve palsy
3. Increased cerebral spinal fluid opening pressure but otherwise normal cytologic and chemistry values
4. Normal symmetric ventricles must be demonstrated by neurological imaging.

IN A NUTSHELL

1. Pseudotumor cerebri is a clinical syndrome with raised intracranial pressure in the absence of space-occupying lesion or apparent obstruction to the CSF pathways.
2. It may occur secondary to many drugs, neurological or systemic illnesses, and certain endocrine/metabolic derangements.
3. Bulging anterior fontanel and headache are the main presentations in infants, and children, respectively.
4. Visual loss is the main concern and complication necessitating therapy.
5. Treating the underlying cause, serial lumbar punctures, acetazolamide, are fenestration of optic sheath, are the few treatment modalities.

MORE ON THIS TOPIC

Benzimra JD, Simon S, Sinclair AJ, Mollan SP. Sight-threatening pseudotumour cerebri associated with excess vitamin A supplementation. Pract Neurol; 2014.

Fonseca PL, Rigamonti D, Miller NR, Subramanian PS. Visual outcomes of surgical intervention for pseudotumour cerebri: optic nerve sheath fenestration versus cerebrospinal fluid diversion. Br J Ophthalmol. 2014;98:1360-3.

Horton JC. Acetazolamide for pseudotumor cerebri: evidence from the NORDIC trial. JAMA. 2014;311:1618-9.

Liguori C, Romigi A, Albanese M, et al. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2014;82:1752-3.

Rogers DL. A review of pediatric idiopathic intracranial hypertension. Pediatr Clin North Am. 2014;61:579-90.

Sinclair AJ, Woolley R, Mollan SP. Idiopathic intracranial hypertension. JAMA. 2014;312:1059-60.

Wall M, Corbett JJ. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2014;83:198-9.

Section 43 NEUROMUSCULAR DISORDERS

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Chapter 43.1
Approach to Diagnosis of Neuromuscular Disorders

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Neuromuscular disorder constitutes a broad category of diseases that impair the function of skeletal muscles. Neuromuscular disorders constitute a significant proportion of pediatric neurological diseases. Broadly it is classified based on neuroanatomical site of lesion into anterior horn cell disease, neuropathy, disorders of neuromuscular junction and myopathy **(Fig. 1)**. It could result from either a genetic defect in structure of muscle (congenital myopathy and muscular dystrophy) or acquired defect (dermatomyositis) **(Flow chart 1)**.

Common clinical presentations in pediatric neuromuscular (NM) diseases include floppy infant and difficulty in walking. Floppy infant presentation may vary from subtle delay in attainment of motor milestones to severe manifestations like respiratory distress with or without diaphragmatic weakness, feeding difficulty and hypotonia. On other hand, older children with neuromuscular weakness may present with difficulty in walking, abnormal gait, enlargement of muscles or pain in muscles or recurrent chest infection. Other clinical presentations of neuromuscular disorders include effort intolerance, easy fatigability and acute rhabdomyolysis.

Weakness refers to loss of muscle strength. In common parlance, it needs to be differentiated from fatigue and asthenia which are common among those with systemic illness. Fatigue refers to inability to perform the task repeatedly, resulting from lack of energy. Similarly, the term asthenia is used for exhaustion without any neuromuscular weakness. Pediatric NM disease may present with involvement of specific group of muscles like facial, bulbar, respiratory, neck muscles, proximal or distal appendicular muscles. Precise neuroanatomical localization is essential for basic approach to clinical thinking and laboratory approach.

Flow chart 1 Broad classification of pediatric neuromuscular disorders based on etiology
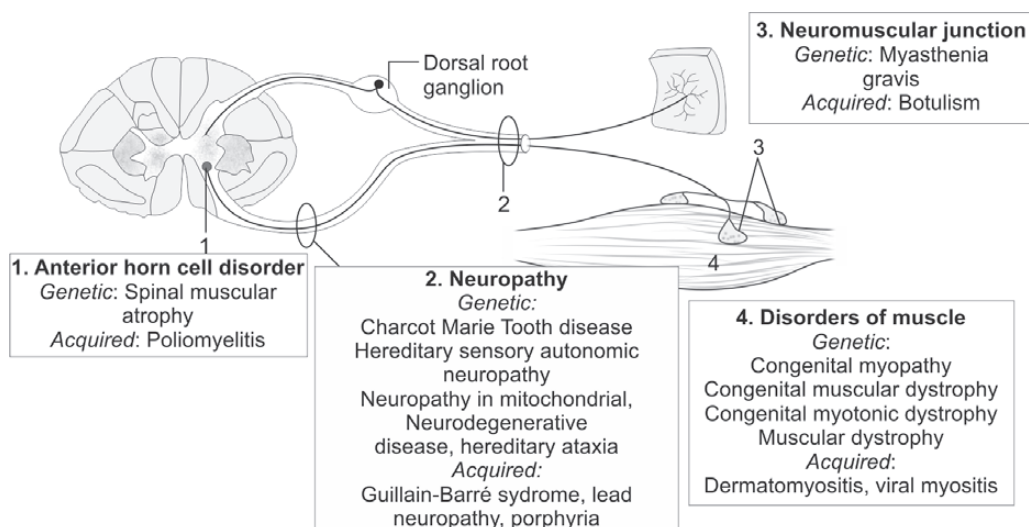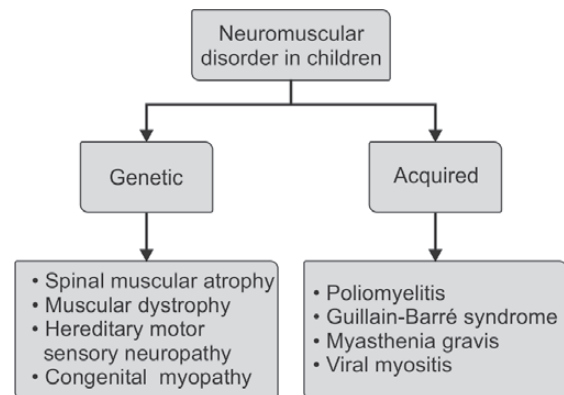
Figure 1 Schematic approach to site of lesion (neuroanatomical localization) in pediatric neuromuscular disorders

NEUROANATOMICAL LOCALIZATION

Precise diagnosis of neuromuscular disorder requires thorough history, focused examination and thoughtful choice of correct investigation. Accurate localization in nervous system is the key approach to neuromuscular disorders. Neuromuscular disorders result from a defect in motor unit comprised of anterior horn cells, axons, nerve, neuromuscular junction and muscle fiber.

Presence of generalized weakness with absent deep tendon reflexes (DTR), with presence of tongue fasciculation points to anterior horn cell pathology. Most of plexopathy or neuropathy will have distal muscle weakness, diminished DTR with or without sensory involvement. In contrast, disorders of neuromuscular junction manifest with ptosis, restriction of extraocular movements, and possibly proximal girdle weakness with normal DTR. Presence of symmetrical proximal girdle weakness with normal or diminished DTR points to myopathy **(Table 1)**. Neuromuscular weakness that results from upper motor neuron disease will manifest with hypertonia, brisk DTR, extensor plantar response and weakness involving antigravity muscles with flexors of lower limb and extensors of upper limb. Clinical symptoms vary according to site of involvement [central nervous system (CNS), anterior horn cell, nerve, neuromuscular junction or muscle].

Clinical Correlate: Neuroanatomical Localization

Floppiness or hypotonia in an infant could result from either a defect in CNS or defect in motor unit. Presence of hypotonia out of proportion to weakness along with normal or brisk DTR and extensor plantar response indicates central cause of floppiness. Similarly, presence of seizures, cognitive impairment and dysmorphism favors central cause. In contrast, presence of weakness, hypotonia, hyporeflexia or areflexia with flexor plantar response indicates motor unit dysfunction. In general, floppy but strong baby has CNS pathology whereas floppy and weak baby has motor unit pathology. Presence of areflexia with tongue fasciculation indicates anterior horn cell involvement (neuronopathy).

In general, proximal weakness is an indicator of myopathy (except congenital myotonic dystrophy) whereas distal weakness goes in favor of neuropathy [exception is spinal muscular atrophy (SMA) type III]. Most of myopathies have symmetrical weakness. Wasting of muscle could result from long-standing myopathy or secondary to neuropathy. Muscular hypertrophy could result from wide range of neuromuscular disorders like Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), myotonia congenita, or SMA type III, or cysticercosis. Presence of fasciculations is an indicator for involvement of anterior horn cells classically seen in SMA.

Table 1 Localization of neuromuscular weakness

Clinical features	Anterior horn cell	Nerve	Neuromuscular junction	Muscle
Weakness	P = D	D > P	P = D	P > D
Muscle atrophy	Yes	Yes	No	Late stages
Tone	Decreased	Decreased	Decreased	Decreased
DTR	Absent	Absent or diminished	Normal or diminished	Normal or diminished
Plantar response	Mute or flexor	Flexor	Flexor	Flexor
Sensation	Normal	Diminished	Normal	Normal

Abbreviations: P, proximal; D, distal.

Disorders of neuromuscular transmission cause fatigable weakness with predilection for cranial and proximal muscles. In children with plexopathy like brachial plexus injury, both proximal and distal muscles are involved with diminished sensation and DTR. Presence of sensory loss, distal atrophy resulting in stork like legs with absent DTR and foot deformities like hammer toe are hallmark for hereditary neuropathies like hereditary motor sensory neuropathy.

Clinical Approach by History

Eliciting an appropriate history gives major clue to diagnosis of underlying neuromuscular disorder. History should address following points: age at onset, whether the illness is progressive or static, is it confined to neuromuscular alone or whether CNS is also involved.

Birth history History begins from antenatal history of decreased fetal movement or polyhydramnios which indicates congenital onset of neuromuscular weakness as seen in congenital myopathy or congenital myotonic dystrophy. Birth history of weak cry at birth, history of being floppy, feeding difficulty, respiratory distress with prolonged ventilatory support and difficulty in weaning in neonatal period are pointers of neuromuscular disease. Other points to elicit in birth history include breech presentation, presence of congenital dislocation of hip and early contractures.

Developmental history Developmental domains should be assessed in all four domains: (1) gross motor, (2) fine motor, (3) cognitive domain and (4) language domain. Presence of developmental dissociation with isolated motor delay with preserved cognition and language again favors neuromuscular disorder. Coexistence of cognitive delay, language/speech delay, vision, hearing impairment or presence of seizure is an indicator towards CNS involvement. It is not uncommon to have muscular disease along with CNS involvement as in DMD, alpha dystroglycanopathies [including Fukuyama congenital muscular dystrophy (CMD), myotonic dystrophy and mitochondrial disease.

Presenting complaints Broadly, neuromuscular complaints could be divided into negative symptoms (weakness, fatigue, exercise intolerance, muscle atrophy) and positive symptoms (myalgia, cramps, contractures, myotonia, myoglobinuria, pain and paresthesia). History of abnormal gait, frequent falls, difficulty in getting up from the floor and difficulty in climbing stairs point towards muscular dystrophy. Pain is uncommon in most of pediatric neuromuscular disorder except in dermatomyositis and polyradiculoneuropathy. Muscle cramps and muscle stiffness are nonspecific complaints, unless when precipitated by exercise and associated with myoglobinuria.

Family history History of consanguinity should be enquired and a three generation pedigree should be made to look for inheritance pattern **(Table 2)**. In the family history, enquire if any of family members use wheelchair, has spinal or skeletal deformity or has any functional limitations. History of early deaths and familial cardiac disease should also be elicited.

Age at onset Neuromuscular weakness which manifest at birth and early neonatal period include SMA, congenital myotonic dystrophy, congenital myopathy, CMD, congenital myasthenic syndrome, glycogen storage disease and carnitine deficiency. Whereas, other muscular dystrophies, inflammatory myopathy, metabolic myopathy could manifest in early childhood.

Onset of weakness Neuromuscular weakness could be acute, subacute or insidious in onset **(Flow chart 2)**. Acute onset of generalized neuromuscular weakness could include acute inflammatory polyradiculoneuropathy, acute infectious myositis or secondary to neuromuscular blockade as in botulism and

Table 2 Inheritance pattern in neuromuscular disorders

Inheritance pattern in neuromuscular disorders	
Autosomal dominant	FSHD, LGMD, OPMD, myotonic dystrophy
Autosomal recessive	LGMD and metabolic myopathy
Maternal transmission	Mitochondrial myopathy
X-linked recessive	Duchenne, Becker and EDMD

Abbreviations: FSHD, facioscapulohumeral muscular dystrophy; LGMD, limb-girdle muscular dystrophy; OPMD, oculopharyngeal muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy.

Flow chart 2 Classification of neuromuscular disorders based on temporal pattern of evolution
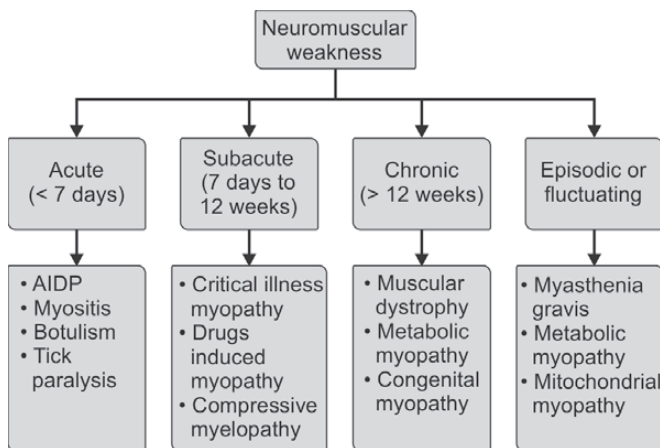
tick paralysis. Weakness secondary to drugs (steroid induced myopathy) and prolonged intensive care unit stay (critical illness myopathy) could be subacute in onset. Most of other neuromuscular illness including muscular dystrophy, endocrinal (hypothyroid) myopathy and metabolic myopathy have insidious onset.

Any neuromuscular weakness with acute or subacute progression indicates underlying systemic illness or when associated with muscle pain could suggest inflammatory myopathy like dermatomyositis. Fluctuating weakness with waxing and waning course is highly suggestive of mitochondrial myopathy, myasthenia and inflammatory myopathy like juvenile dermatomyositis. Episodic weakness with complete recovery strongly suggests metabolic myopathy (glycolytic enzyme defects) or ion channel disturbance (channelopathies like periodic hypokalemic paralysis) or myasthenia.

Progression of weakness Progression of weakness could be slowly progressive or rapidly progressive or may have fluctuating or episodic course. Most of neuromuscular disorders including muscular dystrophy and neuronopathies like SMA have slow progression. Most of neonatal onset weakness including congenital myopathy, congenital myotonic dystrophy and congenital myasthenia are nonprogressive with gradual improvement in the functional ability with appropriate intervention. Disease progression is often superimposed by normal development; as a result parents report stabilization or rather improved function even among children with progressive muscular dystrophy. Moreover, seasonal improvement is often noted with outdoor activity, rather outdoor activity including water sports are known to improve the neuromuscular function.

Extent of involvement Weakness in children could manifest with frequent falls, tripping over floor, stamping gait and difficulty in walking suggestive of distal lower limb weakness. They could present with difficulty in getting up from floor or from toilet or low lying chair (hip flexor weakness) and walking upstairs (hip extensor weakness) and downstairs (quadriceps weakness) suggestive of proximal lower limb weakness. The upper limb weakness could present with inability to lift the arm (proximal shoulder girdle weakness) or inability to hold the objects, poor hand grip, poor handwriting and inability to button and unbutton shirt (distal).

Weakness could also manifest with inability to lift head off the bed while attempting to get up from lying down position (neck flexor weakness), inability to sit up from lying down position (truncal weakness), drooping of eyelids (ptosis), diplopia (extraocular muscle weakness), and difficulty in deglutition or nasal regurgitation of feeds (bulbar weakness). Dull facial expression, wasting of temporalis muscle, failure to close the eyes completely, inability to purse the lips, inability to clear food particle caught between lips and gums, inability to suck from a straw or blow balloons is marker towards facial weakness. Presence of slurred speech with difficulty in pronouncing words *d, n, l* and *t* points to tongue muscle weakness. Presence of respiratory distress with paradoxical breathing and dyspnea indicate diaphragmatic weakness. Truncal weakness will manifest with inability to get up from lying down position and prolonged immobilization leads to scoliosis. History of diurnal variation, rapid fluctuation of weakness with febrile illness is pointer towards myasthenia and other neuromuscular junction abnormalities. **Figure 2** summarizes the extent of neuromuscular involvement.

Other presenting features History of muscular pain is common among children with inflammatory myopathy like dermatomyositis or polymyositis or acute infective viral or bacterial myositis. Adolescent female presenting with limb-girdle weakness and pain with presence of violaceous discoloration of eyelid and punctate ulceration in extensor surface of limbs is hallmark presentation of juvenile dermatomyositis. History for presence of rash, joint pain should be elicited to look for connective tissue disorders. Medication history should be carefully elicited **(Table 3)**.

Postexertional pain or muscular cramps with or without history of myoglobinuria (passage of red-colored urine) is an indicator towards metabolic myopathy. Exaggeration of muscle stiffness with cold is known with paramyotonia congenita. Presence of diurnal variation, worsening with febrile illness, prominent extraocular symptoms and ptosis is a marker towards myasthenia gravis. History of excessive sweating, breathlessness, orthopnea in a child with suspected neuromuscular weakness could suggest cardiomyopathy.

Precipitating factors Weakness precipitated with fever or fasting is suggestive of fatty acid oxidation disorder. The rapid onset of neuromuscular weakness in a previously healthy adolescent precipitated by high carbohydrate meal like following a heavy dinner is pointer towards hypokalemic periodic paralysis. Pain, weakness and passage of red urine (myoglobinuria) following an exercise could lead to possibilities of metabolic myopathy (glycolytic enzyme defect like McArdle disease or myophosphorylase deficiency) or mitochondrial disorders or lipid storage myopathy.

Pattern of weakness There are roughly six patterns of weakness in pediatric neuromuscular diseases **(Table 4)**. Limb-girdle weakness involves proximal muscles of upper and lower limb, along with neck extensor weakness. Majority of neuromuscular disease have this pattern of weakness. Distal weakness is often associated with
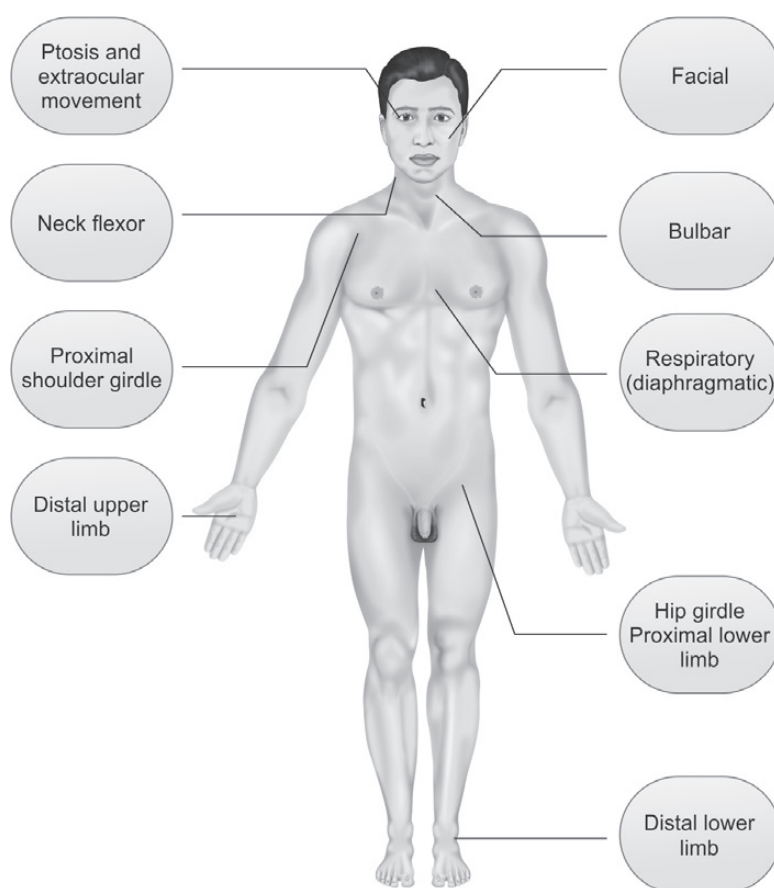
Figure 2 Extent of neuromuscular involvement

Table 3 Common drugs implicated in neuromuscular diseases in children

Myopathy	Neuropathy	Both
Corticosteroids	Cisplatin	Amiodarone
Cyclosporine	Isoniazid	Chloroquine
D-penicillamine	Metronidazole	
Zidovudine	Phenytoin	
	Pyridoxine	
	Vincristine	

distal atrophy more common with neuropathy and few distal myopathies **(Table 4)**. Scapuloperoneal muscle weakness refers to involvement of parascapular muscles of proximal arm and anterior compartment of leg. Other patterns are fairly specific for certain neuromuscular disease as outlined in **Table 4**. **Figures 3A to D** depicts the pattern of weakness in muscular dystrophy.

Associated systemic involvement One should look for associated systemic complications including cardiac involvement as seen in DMD, BMD, Emery-Dreiffuss muscular dystrophy and acid maltase deficiency. Respiratory muscle (intercostal and/or diaphragmatic) weakness is seen among children with congenital myopathies, CMD, spinal muscular atrophy and more rarely in mitochondrial disorders, congenital or inflammatory myopathy. Hepatic involvement is observed among mitochondrial disorders, acid maltase deficiency, debranching enzyme deficiency and carnitine deficiency. Presence of facial dysmorphism could suggest congenital myopathy. Ocular involvement is common in congenital myotonic dystrophy, CMD and mitochondrial disorder.

Examination

Vitals One should look for clinical evidence of tachycardia, tachypnea and respiratory distress with paradoxical breathing which may point to diaphragmatic weakness. Presence of features of congestive heart failure in a child with neuromuscular weakness could be an indicator of underlying cardiomyopathy. Recording baseline blood pressure is essential before starting corticosteroid therapy in children with DMD.

Anthropometry Children with inherited neuromuscular diseases often have wasting of muscles leading to chronic malnutrition. At the same time, children with dystrophy who become nonambulatory have a tendency to gain weight. Monitoring anthropometric parameters is essential for appropriate intervention.

General physical examination Presence of heliotrope rash over eyelids along with Gottron papules in the knuckles in a child with progressive painful proximal myopathy is suggestive of dermatomyositis **(Figs 4A and B)**. Clinical features of facial dysmorphism or neurocutaneous markers could suggest a co-existing CNS involvement. Respiratory involvement can be assessed bedside by asking the child to count to 50 in a single breath (single breath count test).

Neurological examination Intelligence and cognitive ability needs assessment. Gait and posture needs to be assessed by asking the patient to stand with feet closed, standing and walking on heels and toes, rising from low chair or squatting posture without using arms and rising from supine to sitting without arm. These maneuvers will elicit soft neurological weakness which might often be missed with routine neurological examination.

Table 4 Patterns of neuromuscular weakness in children

Pattern of weakness	Differentials
Progressive proximal limb-girdle weakness	• Muscular dystrophy (Bethlem myopathy, dystrophinopathy, FSHD) • Inflammatory myopathy (dermatomyositis, polymyositis) • Juvenile spinal muscular atrophy • Metabolic myopathy (acid maltase def, carnitine def, debrancher enzyme def, mitochondrial myopathy) • Endocrine myopathy
Progressive distal limb weakness	• *Congenital myopathy:* Nemaline rod, central core, centronuclear myopathy • Muscular dystrophy (EDMD, FSHD) • Neuropathy (CMT, giant axonal neuropathy, drug induced, systemic vasculitis) • Distal myopathy (myotonic dystrophy)
Scapuloperoneal weakness	• Scapuloperoneal dystrophy • Emery-Dreifuss dystrophy • LGMD 1B (laminopathy) • LGMD 2A (calpainopathy) • LGMD 2C-F (sarcoglycanopathies) • LGMD 2I (FKRP)
Ptosis	Myasthenia gravis, centronuclear and nemaline rod myopathy, myotonic dystrophy
Ptosis and ophthalmoplegia	Progressive external ophthalmoplegia, oculopharyngeal muscular dystrophy, myasthenia gravis, Lambert-Eaton syndrome
Prominent neck extensor weakness	• Dermatomyositis • Polymyositis • Facioscapulohumeral dystrophy • Myotonic dystrophy types 1 and 2

Abbreviations: FSHD, facioscapulohumeral dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; CMT, Charcot-Marie-Tooth; LGMD, limb-girdle muscular dystrophy; FKRP, Fukutin-related protein gene; def, deficiency.
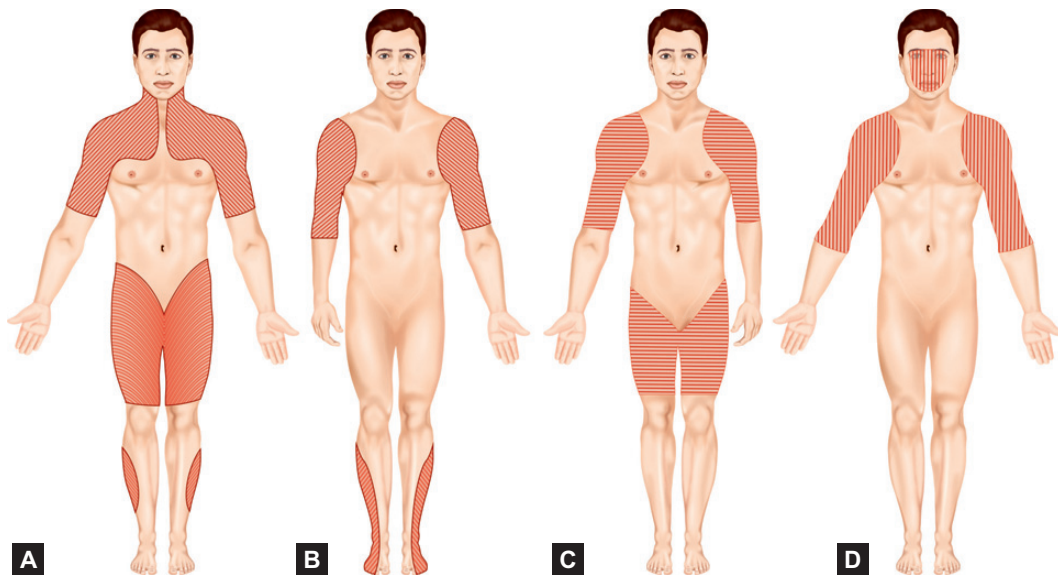
Figures 3A to D Patterns of weakness in muscular dystrophy. (A and C) Proximal limb-girdle weakness seen among DMD and LGMD; (B) Scapuloperoneal weakness seen among EDMD and (D) Facioscapulohumeral weakness seen in FSHD
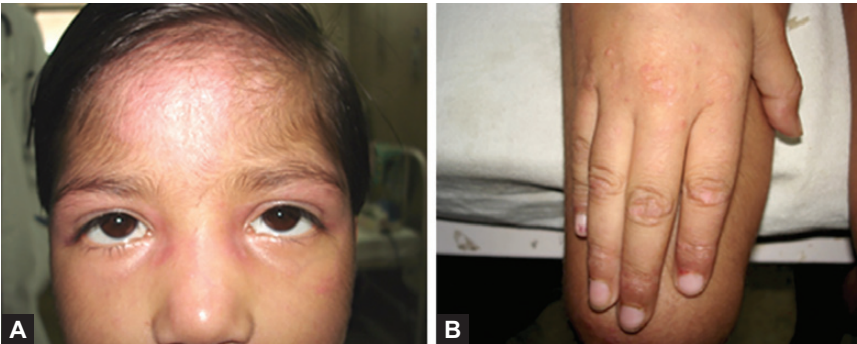
Figures 4A and B Periorbital heliotrope rash (A) and Gottron papule (B) along the knuckles of hands in a child with juvenile dermatomyositis

- Look for gait (ambulatory) and posture (nonambulatory):
  – Waddling gait with proximal myopathy like DMD (Gowers' sign)
  – Waddling gait and lordotic posture is suggestive of proximal hip girdle weakness observed among children with muscular dystrophy
  – Stamping gait (or weakness of foot dorsiflexor) is common among peripheral neuropathy
  – Toe walking is an indicator of muscular dystrophy, spinal dysraphism, spastic diplegia or a normal variant. It can be secondary to early ankle contractures as seen in children with calpainopathy **(Fig. 5)**.
  – Lordotic posture is a marker of proximal girdle weakness
  – Gowers' sign is an indicator of proximal hip girdle weakness **(Figs 6A to D)**.
- *Look for active and passive tone* Hypotonia with areflexia is a pointer towards involvement of motor unit (myopathy, neuropathy, NM disorders) whereas hypotonia with brisk reflexes is pointer towards CNS etiology. Look for features of myotonia in child and parents (congenital myotonic dystrophy).
- *Look for clinical features in face* Asymmetric/Oblique smile [facioscapulohumeral muscular dystrophy (FSHD)] **(Fig. 7)**, ptosis (myasthenia gravis), ophthalmoplegia [Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia (CPEO)] and myotonia of eyelid (myotonia congenita).
- *Clinical features in upper limb and trunk* Neck flexor weakness (DMD), paraspinal contractures (rigid spine syndrome),

winged scapula (FSHD), contractures of elbow (Emery-Dreifuss muscular dystrophy) and hyperextensibility of distal joints as seen in Ullrich variant of CMD **(Fig. 8)**. Winging of scapula is demonstrated in **Figure 9**.

- *Clinical features in lower limb* Inverted Champagne bottle (peroneal muscular atrophy), hypertrophy of extensor digitorum brevis (EDB) (DMD) **(Fig. 10)**, pes cavus (Friedreich's ataxia) and talipes equinovarus (DMD). Pes cavus deformity is demonstrated in **Figure 11**.
- Examine the mother for evidence of myotonia (ask her to close her fist and then open it suddenly) and features of myasthenia (ptosis, weakness).
- Look for wasting of muscles including sternocleiodomastoid muscle, trapezius muscle, winging of scapula and atrophy of intrinsic muscles of hands.
- Look for exaggerated lumbar lordosis. Wasting of quadriceps muscle, anterior compartment of legs, tapering of legs distally, tightness of heel cords, pes cavus, pes planus and presence of foot drop **(Fig. 11)**.
- Look for retinopathy, deafness, cardiac dysfunction, respiratory insufficiency, visceral enlargement and any other clue susceptible to guide the clinician's assessment.

Analysis of the case at the end of history and examination is briefly summarized in **Table 5**. An algorithm suggested for analysis of muscle disease is outlined in **Flow chart 3**.

Figure 5 Classical ankle contracture in a child with calpainopathy

Figure 7 Expressionless facies, proximal shoulder girdle weakness and atrophy of scapulohumeral distribution seen in facioscapula humeral dystrophy (FSHD)

Figures 6A to D Gower's sign: Figure depicting the proximal weakness involving the hip girdle muscle where the child when attempts to stand from sitting position, child takes the support and climbs on his own legs
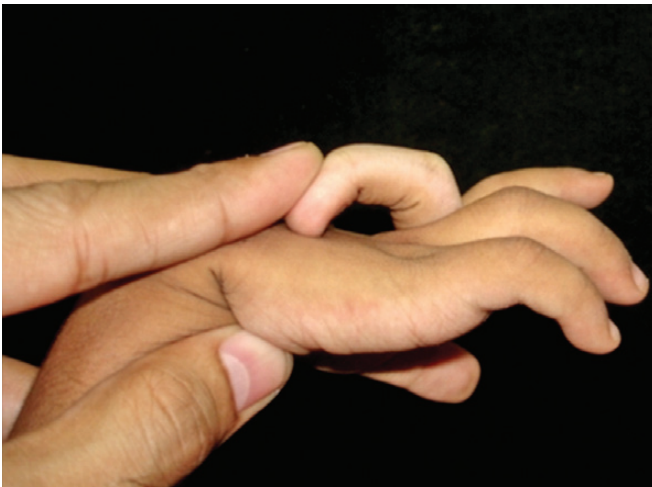
Figure 8 Hyperextensibility of distal joints of hand seen in Ullrich muscular dystrophy

Figure 9 Weakness of serratus anterior muscle resulting in winging of scapula

Figure 10 Calf hypertrophy in a child with dystrophinopathy
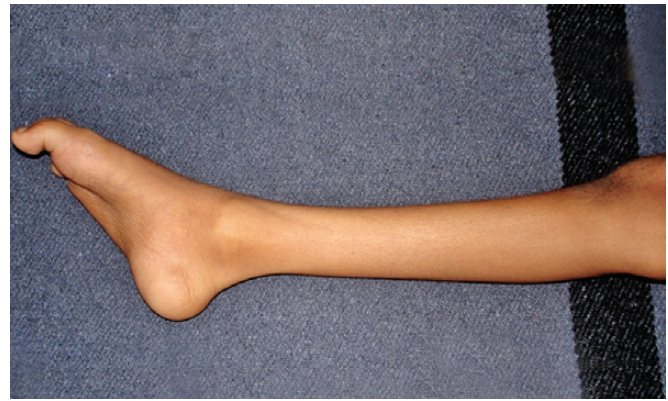
Figure 11 Distal foot muscle atrophy with high arched foot deformity (Pes Cavus) with fixed deformity involving flexion contracture of second, third and fourth toe (Hammer toe)

LABORATORY INVESTIGATIONS

Basic laboratory approach to neuromuscular disorders is outlined in **Flow chart 4**. **Flow chart 5** depicts the approach to a child with progressive symmetrical proximal muscle weakness (DMD phenotype). Over all laboratory investigations essential for diagnosis of neuromuscular disorders are as follows:

Preliminary Investigations

Preliminary investigations including routine hematological and biochemical investigations may give certain clue to neuromuscular disease. For example, presence of raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and total leukocyte count (TLC) might indicate dermatomyositis. Electrolyte abnormalities especially hypokalemia and hyperkalemia are associated with periodic paralysis. Raised serum creatinine phosphate kinase (CPK), urine myoglobinuria, hyperkalemia, raised aldolase, lactate dehydrogenase (LDH) and aspartate aminotransferase [serum glutamate-pyruvate transaminase (SGPT)] could indicate rhabdomyolysis or simply muscular dystrophy.

Specific Clinical Tests

In children with suspected myasthenia with equivocal repetitive nerve stimulation test (RNST) findings, neostigmine challenge test can be performed. In this test, subcutaneous (SC) injection of

Table 5 Analysis and summary of clinical findings based on history and examination

Analysis based on history and examination
1. *Age at onset*: Neonatal, infantile, early childhood, school aged or adolescent
2. Proximal weakness or distal weakness
3. *Extent of weakness*: Look for involvement of arms, legs, trunk, neck flexor, neck extensor, extraocular muscle, ptosis, bulbar muscles and respiratory system weakness
4. *Progression of weakness*: Nonprogressive versus progressive weakness; if progressive whether rapid or slow progressive
5. *Current functional status*: Based on GMFM classification
6. *Inheritance pattern*: Autosomal dominant, autosomal recessive, X-linked dominant or X-linked recessive inheritance

Flow chart 3 Algorithm for suspected muscle disorders
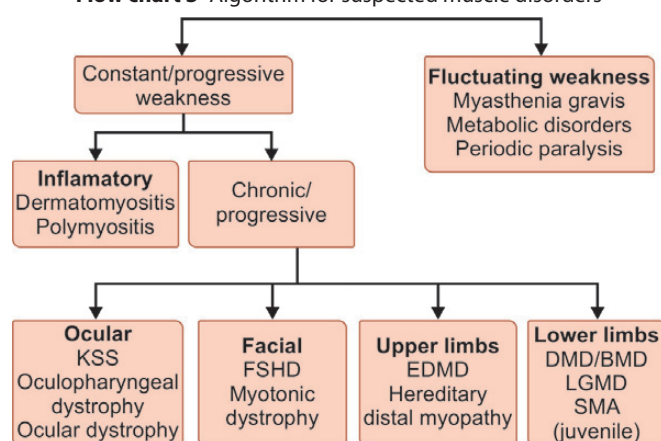
Abbreviations: KSS, Kearns-Sayre syndrome; FSHD, facioscapulohumeral muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, limb-girdle muscular dystrophy; SMA, spinal muscular atrophy; dys, dystrophy.

neostigmine is administered under strict ECG and vital monitoring to look to objective improvement in ptosis (measured by scale with serial photographs for 15 min every 3 min).

In children with suspected metabolic myopathy, forearm ischemic test is performed. Baseline arterial lactate and blood ammonia are obtained. A sphygmomanometer is applied on the arm and pressure is raised just above systolic blood pressure. The patient is asked to exercise with hands repeatedly for minimum of 1 min or till maximum fatigue. The cuff is deflated, blood samples

Flow chart 5 Broad approach to diagnosis of children with symmetrical progressive proximal weakness
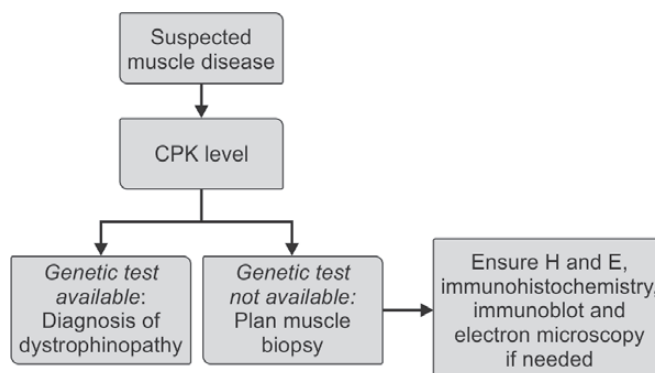
for lactate and ammonia are obtained at 1 min, 3 min, 6 min and 10 min. In normal healthy patient and in children with lipid storage disorder, lactate levels increase initially for first two readings followed by decline. In children with McArdle disease, normal rise in lactate is absent. Normal rise in lactate with no rise in ammonia suggests myoadenylate deaminase deficiency.

Creatine Phosphokinase Levels

Most common first-line screening investigation in neuromuscular weakness is elevated in inflammatory muscle disease (dermatomyositis, polymyositis) and active primary muscle disease [DMD, BMD, limb-girdle muscular dystrophy (LGMD), CMD]. Moderate elevation is seen among facioscapulohumeral dystrophy, Emery-Dreifuss muscular dystrophy and congenital myopathy.

Flow chart 4 Basic laboratory approach to neuromuscular disorders
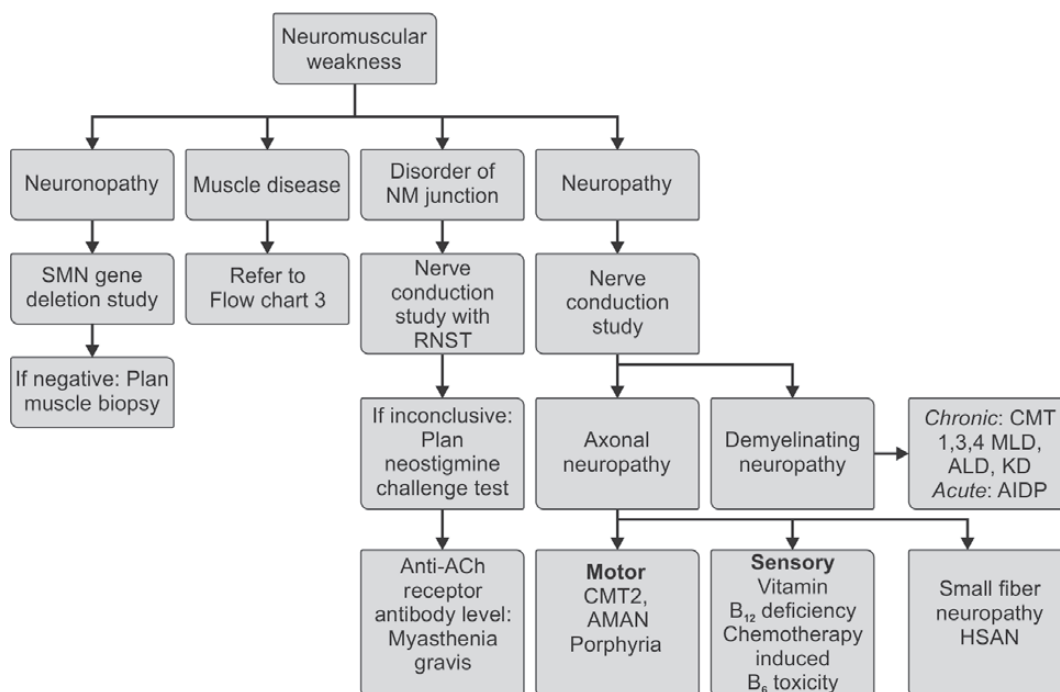
Abbreviations: CMT, Charcot-Marie-Tooth; RNST, repeated nerve stimulation test; HSAN, hereditary sensory autonomic neuropathy; AIDP, acute inflammatory demyelinating polyradiculopathy.

CPK levels are normal or mildly elevated in neuronopathies like SMA. CPK-MM is muscle specific whereas CPK-MB is cardiac specific but may also be increased in myopathy. CPK levels may be increased following trauma and electromyography (EMG) study. Hence, CPK levels must be done prior to EMG study and should be repeated over time. CPK levels may pseudonormalize in end stages of most of dystrophinopathies or if the child is on steroids.

Molecular Diagnostic Testing

Molecular testing has become first line investigation among those suspected with DMD gene deletion) **(Figs 12A and B)**, SMA (*SMN1* gene deletion) **(Figs 13A and B)**, calpainopathy [Calpain 3 western blotting **(Fig. 14)**], congenital myotonic dystrophy (*DMPK* gene defect) or myotubular myopathy (*MTM1* gene defect).

Nerve Conduction Study Including Needle EMG

Neurophysiological examination of young children is difficult to apply in young and uncooperative children. It would be useful in differentiating site of lesion (nerve, muscle, neuromuscular junction) and for diagnosing myotonia. RNST can be performed to look for evidence of myasthenia. Needle EMG will assess muscle spontaneous activity, response to insertion of probe, characterization of motor unit action potential (MUAP), and rapidity with which additional motor units are recruited in response to electrical signal. EMG showing evidence of brief duration, small amplitude motor unit with increased recruitment is suggestive of myopathy. Of note, reduced NCV can be seen in patients with primary muscle disorder (CMD with merosin deficiency).

Muscle and Nerve Biopsy

Muscle biopsy is fairly essential for final diagnosis of majority of neuromuscular diseases in children unclassified by genetic testing **(Table 6)**. Muscle biopsy is ideally obtained from vastus lateralis or deltoid. Gastrocnemius muscle is avoided as tendon insertion extends through muscle, which may result in inadvertent sampling of tendon resulting in difficulty in interpretation.
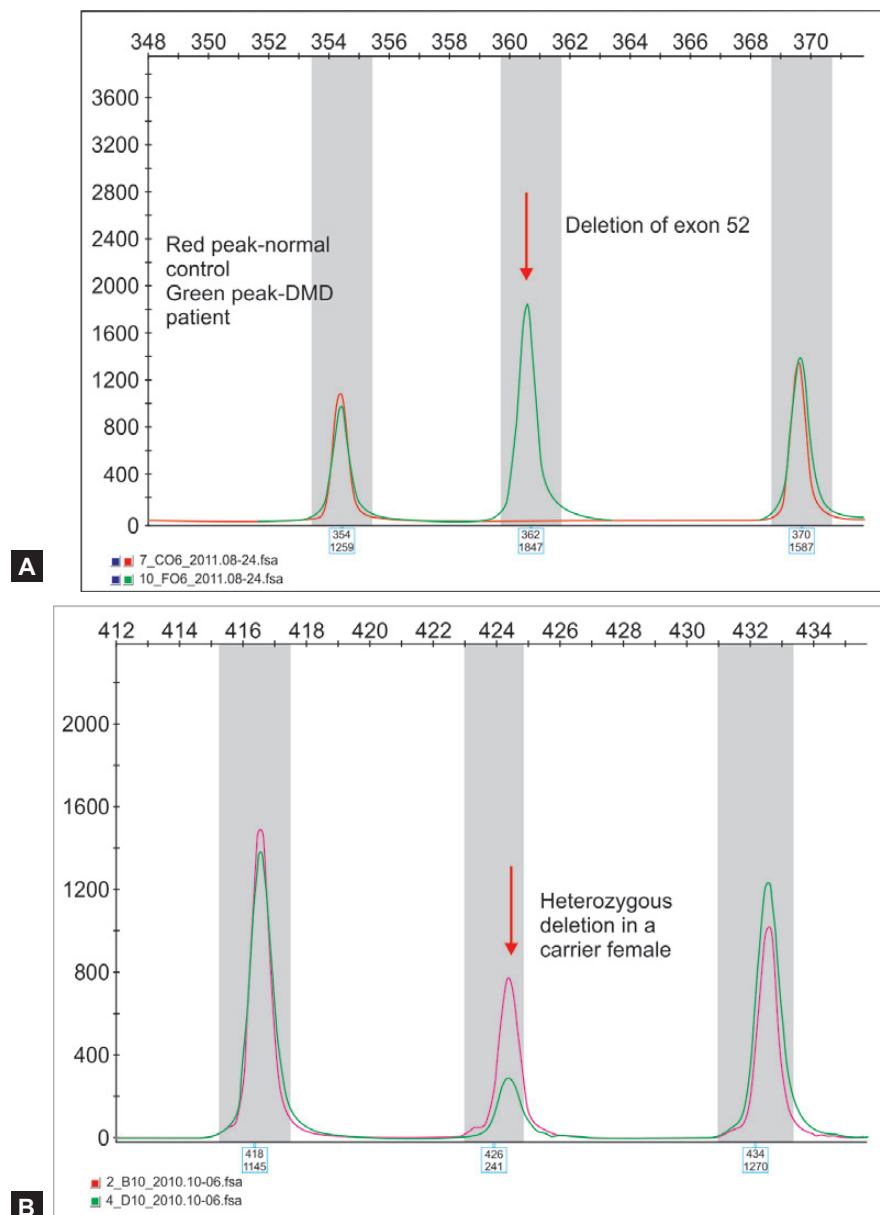
Figures 12A and B (A) Deletion of Exon 52 of *DMD* gene resulting in DMD phenotype; and (B) The heterozygous deletion resulting in carrier state of DMD
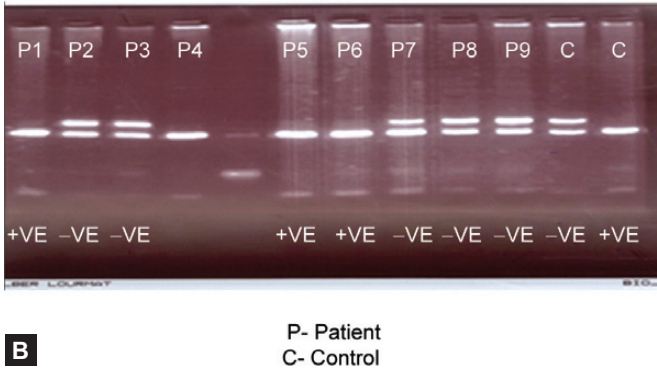
Figures 13A and B (A) A child with spinal muscular atrophy and its confirmation using MLPA; (B) Polymerase chain reaction (PCR) method for analysis of survival motor neuron (SMN) Exon 7 deletion
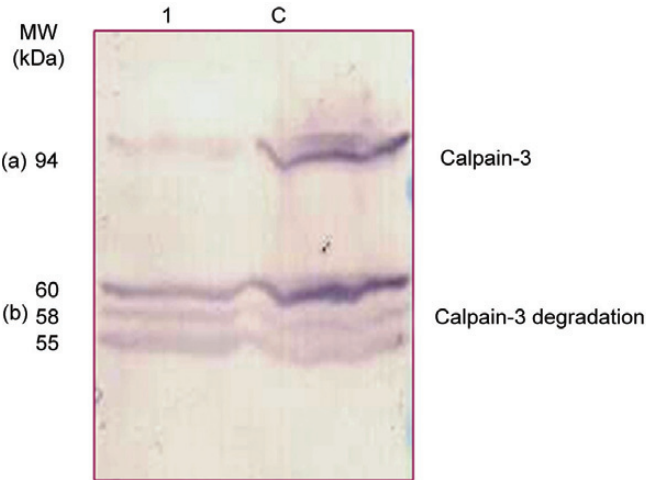
Figure 14 Calpain-3 western blotting using anti-calpain-3 antibody (94 kDa) from patient with suspected calpainopathy. In (a), Control (C) shows band of normal molecular mass and amount. Case 1: partial calpain-3 deficiency; (b) calpain-3 degradation band

Table 6 Key features in muscle biopsy in neuromuscular disorders

Features in muscle biopsy	Neuromuscular disease
Muscle fiber necrosis with regenerative changes and replacement with fat	Dystrophies (DMD, BMD, LGMD)
Ragged red fibers with oxidative enzyme study (NADH, succinate dehydrogenase)	Mitochondrial myopathy
Inflammatory changes with mononuclear infiltrates	Dermatomyositis
Glycogen accumulation with PAS staining	Glycogen storage disease

Biopsy can be obtained by punch biopsy or open biopsy. Most of pathological centers with facilities for immunohisto-chemistry prefer receiving open biopsy samples. Muscle biopsy including immunohistochemical staining is useful in character-ization of muscular disorders [dystrophinopathy **(Figs 15A to D)**, calpainopathy **(Figs 16A to C)**, congenital myopathy **(Figs 17 and 18)** and mitochondrial disorders **(Figs 19 and 20)**]. Electron microscopy is essential for characterization of type of congenital myopathy. Ultrasonography and magnetic resonance imaging (MRI) muscle are good modalities for localizing the best site for muscle biopsy. MRI muscle with short-tau inversion recovery
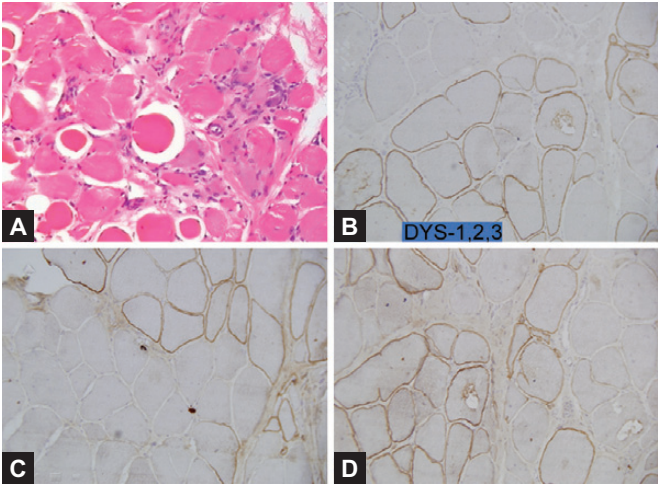
Figures 15A to D Photomicrographs (case of Becker muscular dystrophy) showing features of muscular dystrophy (A, H&E x 400), mosaic pattern of immunostaining for dystrophy 1, 2 and 3 (B, C, D x 400)
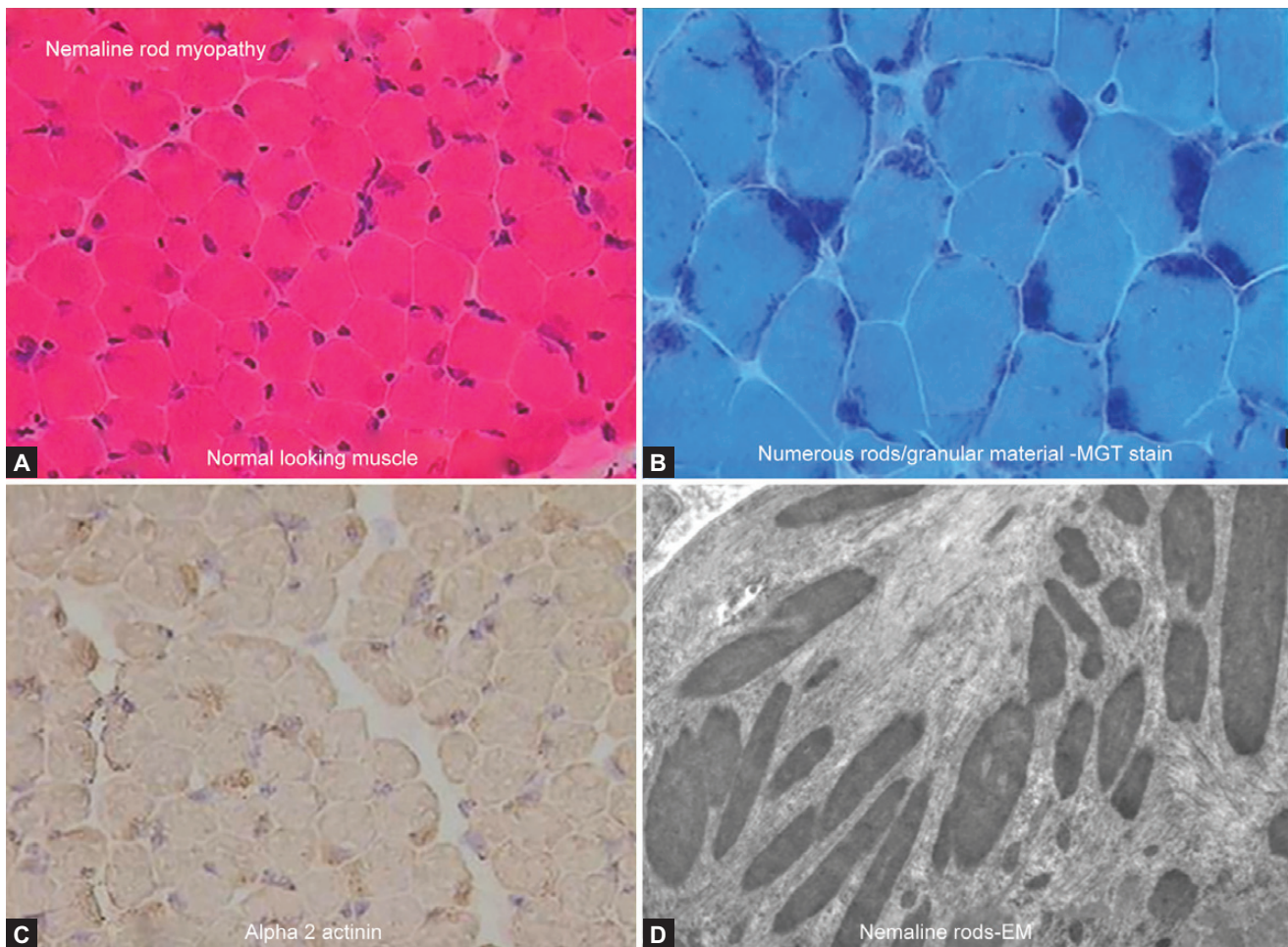
Figures 17A to D Photomicrographs showing normal looking muscle in a patient of nemaline rod myopathy (A, H&E x 200); granular greenish material accruing (B, MGT stain x 400); material is immunoreactive to alfa 2 actinin (C, x 100); ultrastructural examination showed numerous rod like structures (D, x 7,500 original magnification)
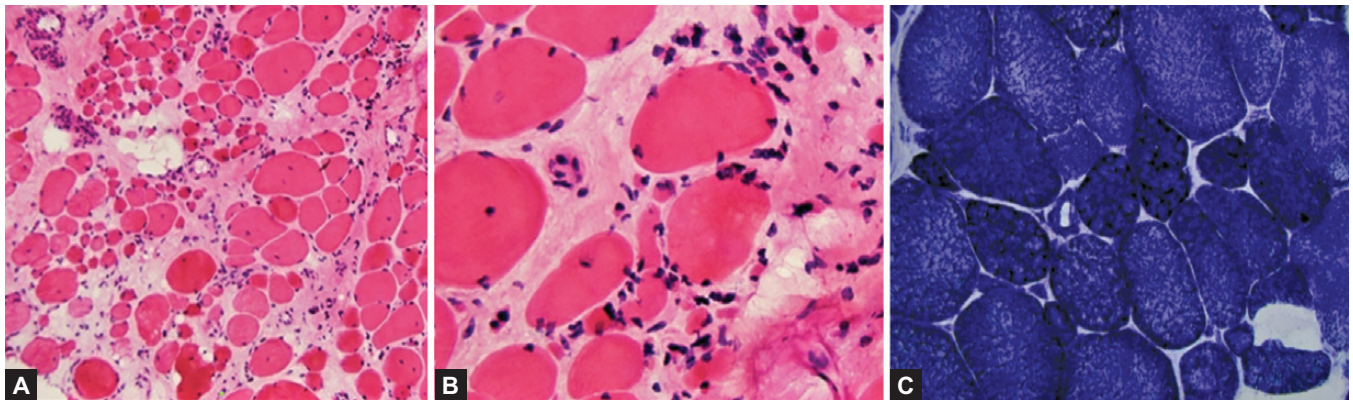
Figures 16A to C Muscle biopsy from a case of calpainopathy showing features of muscular dystrophy (A and B, H&E x 100 and 400 respectively); NADH-TR stain showing numerous lobulated fibers (C, x 400)

(STIR) sequence is especially useful in inflammatory myopathies like dermatomyositis. Nerve biopsy is sometimes useful for diagnosis of hereditary motor and sensory neuropathy (HMSN) where genetic testing (*PMP22* gene deletion) is either not available or not affordable.

Skin Biopsy

It is a simple and less traumatic procedure which requires minimal sedation. It results in less traumatic scar and there are less chances of infection. Muscle biopsy being an invasive procedure and genetic testing facilities being available only in a few centers. Thus,
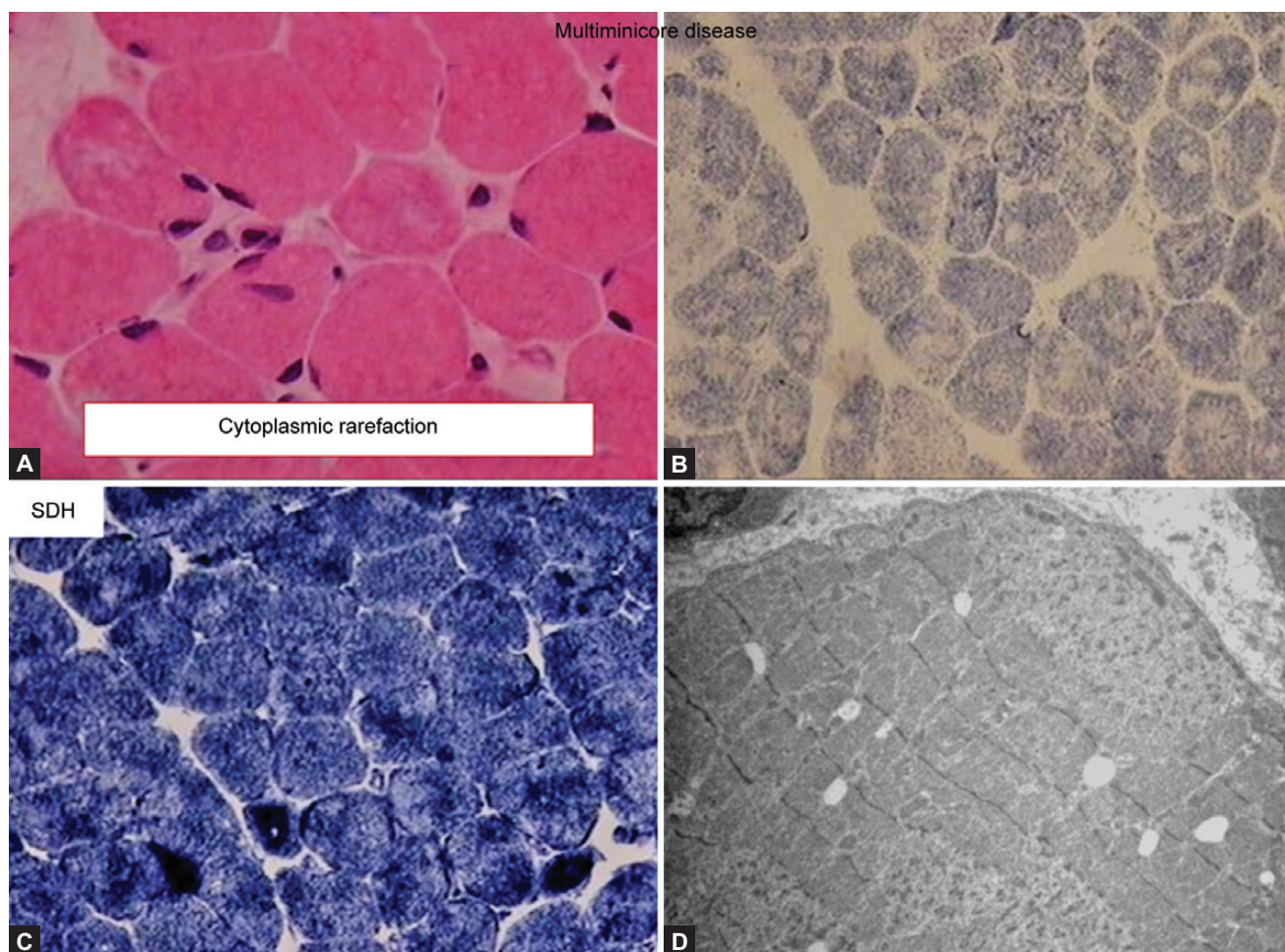
Figures 18A to D Multiminicore disease: Photomicrographs showing rarefaction of the cytoplasm (A, H&E x 400); numerous unstained areas on SDH and NADH-TR staining (B and C x 200); destruction and streaming of Z bands (D, x 1,650 original magnification)
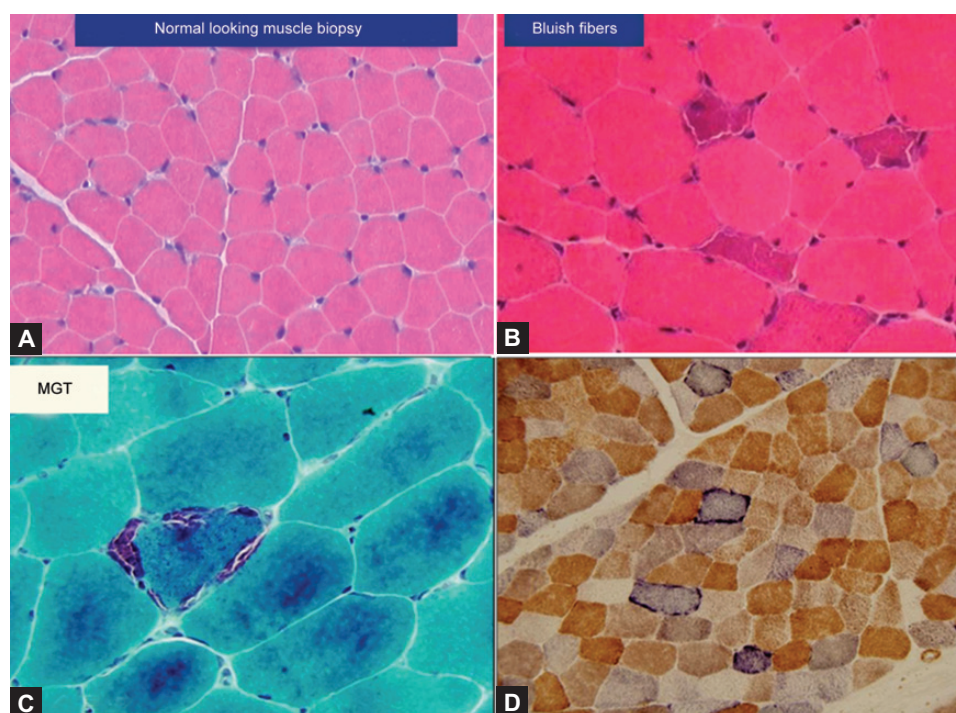
Figures 19A to D: Photomicrographs (case of mitochondrial myopathy) showing normal looking muscle fibers (A, H and E x 200) and bluish fibers which appear as ragged red fibers with MGT stain and COX negative but SDH positive with COX/SDH stain (B and C, x 400; D, x 200)

a diagnostic test that is easily available, simpler, and less invasive is desirable. Over the past 2 decades, skin biopsy has been evolving as a suitable option. Skin biopsy can substitute for muscle biopsy as the preliminary diagnostic tool directing appropriate molecular testing. However, further studies are required to determine if skin biopsy can hold promise for the future. Skin biopsy can be used for screening dystrophinopathy in muscular dystrophy patients (high sensitivity and positive predictive value). It being a simple and minimally invasive procedure, histopathologic and molecular markers of disease progression and response to novel treatment options can be assessed serially **(Figs 21 and 22)**.

Enzyme Analysis

Metabolic myopathy requires enzymatic study for confirmation. Enzyme analysis includes Muscle phosphorylase deficiency (McArdle disease) and acid maltase deficiency (Pompe disease). Tandem mass spectrometry is required for diagnosis of carnitine palmitoyltransferase (CPT) deficiency and other more uncommon metabolic defects.

Antibody Testing

In children with suspected myasthenia gravis, acetyl choline receptor antibody (AchR Ab) and anti-MuSK antibody are essential
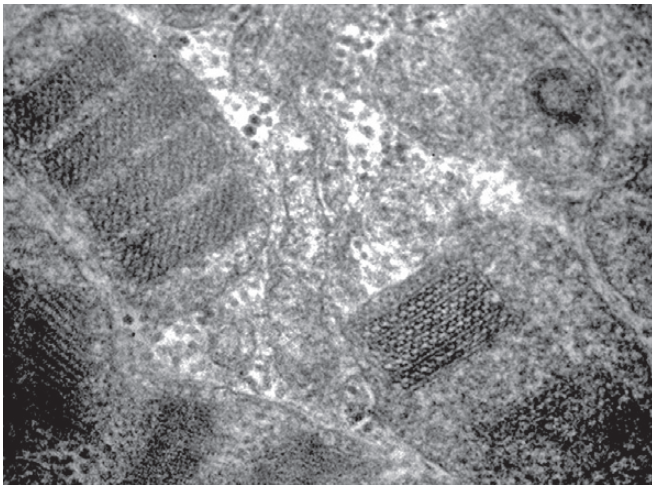
Figure 20 Electron microphotograph showing zipper-like paracrystalline inclusions in the mitochondria (x 8,500 original magnification)
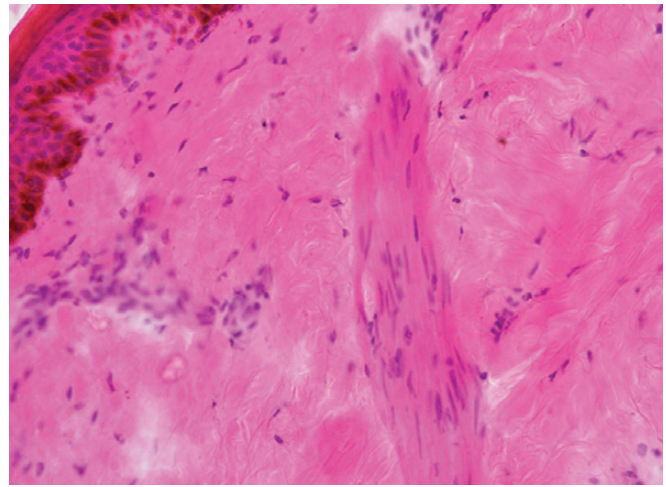
Figure 21 H and E staining of skin biopsy showing arrector pili muscle (H and E x 400)
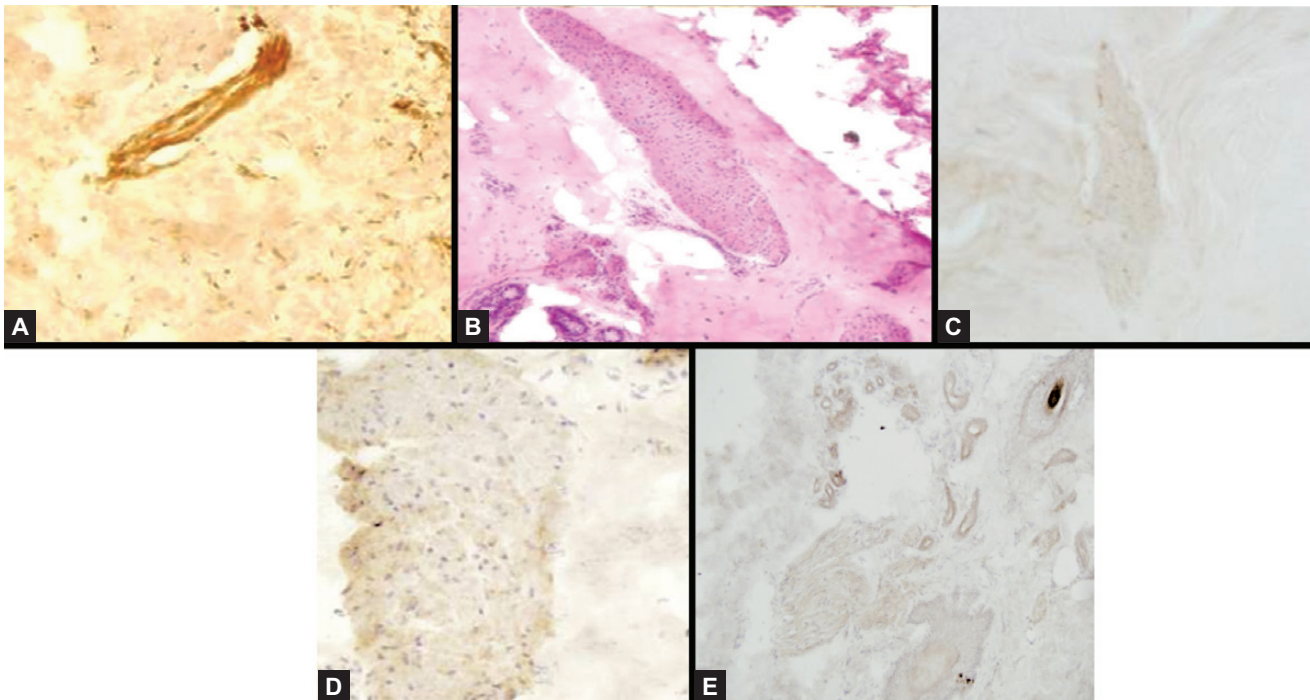
Figures 22A to E Skin biopsy of DMD patient showing normal arrector pili muscle with loss of dystrophin 1, 2, 3 and upregulation of utrophin (H and E x 400)
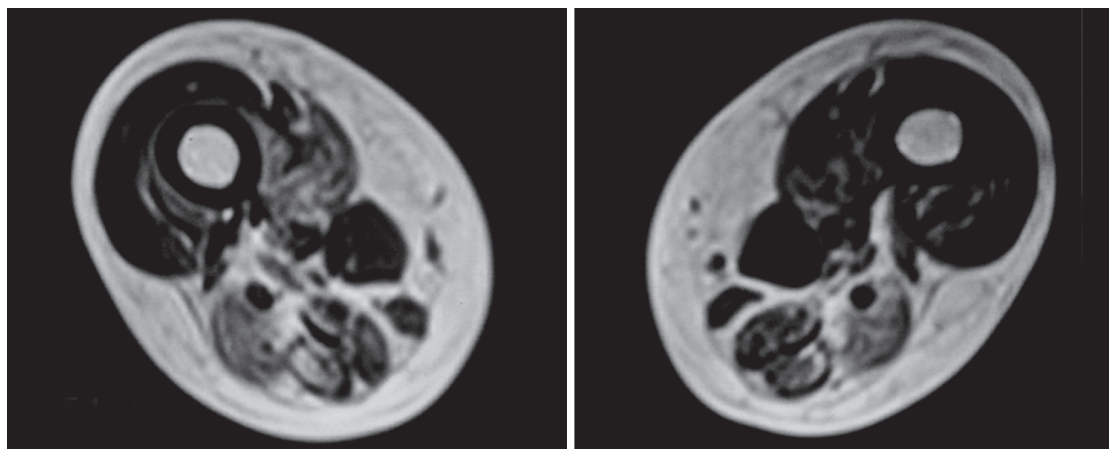
Figure 23 T1-weighted axial MRI image at the level of thigh shows fatty infiltration and atrophy of posteromedial group of muscles in a child with calpainopathy

for diagnosis of juvenile myasthenia gravis. Similarly, antimyositis antibodies (Anti Jo-1, Anti Mi2, Anti Ro 52) are useful supportive investigation for diagnosis of dermatomyositis.

MRI Brain

Central nervous system should be screened among children with merosin deficient CMD and alpha-dystroglycanopathies (Muscle-Eye-Brain disease, WWS, Fukuyama CMD. Magnetic resonance spectroscopy (MRS) is useful in suspected mitochondrial myopathy.

Muscle Ultrasound and Muscle MRI

Magnetic resonance imaging (MRI) and ultrasonography muscle (Neuromuscular imaging) is being used increasingly to characterize the severity and pattern of muscle involvement in inherited neuromuscular disorders. It has emerged as an important noninvasive adjunct to diagnosis of neuromuscular diseases. Although, it is essential to emphasize that muscle biopsy remains the gold standard for establishing the diagnosis. Characteristic patterns on muscle MRI helps in differentiation of dystrophy versus nondystrophic muscle; characterize the pattern (selective involvement of certain group of muscles) for narrowing the differentials in congenital myopathy and LGMD. The patterns of muscle atrophy, intramuscular fibrosis and fatty infiltration can be detected using muscle ultrasonography. In addition, it can visualize the muscle movement, contraction and fasciculations. DMD is known to result in severe inhomogenous increase of muscle echointensity with normal thickness whereas SMA causes inhomogenous increase in muscle intensity with atrophy. Similarly, calpainopathy results in fatty infiltration and atrophy of posteromedial group of muscles **(Fig. 23)**.

MORE ON THIS TOPIC

Arnold WD, Flanigan KM. A practical approach to molecular diagnostic testing in neuromuscular diseases. Phys Med Rehabil Clin N Am. 2012;23:589-608.
Dimberg EL. The office evaluation of weakness. Semin Neurol. 2011;31:115-30.
Jackson CE. A clinical approach to muscle disease. Semin Neurol. 2008;28:228-40.
McDonald CM. Clinical approach to diagnostic evaluation of hereditary and acquired neuromuscular disorder. Phys Med Rehabil Clin N Am. 2012;23:495-563.
Menezes MP, North KN. Inherited neuromuscular disorders: pathway to diagnosis. J Pediatr Child Health. 2012;48:458-65.
Patterson MC, Gomez MR. Muscle disease in children: a practical approach. Pediatr Rev. 1990;12:73-82.
Sagiul A. Evaluation of the patient with muscle weakness. Am Fam Physician. 2005;71:1327-36.

IN A NUTSHELL

1. Neuromuscular commonly presents as floppiness in infancy and gait difficulty with proximal or distal weakness.
2. While approaching a child with suspected neuromuscular disease ascertain its mode of inheritance, onset and progression of weakness, extent of weakness and selective involvement of muscle groups to reach to a broad diagnosis.
3. Once a clinical diagnosis and neuroanatomical localization is made, laboratory investigations should be chosen judiciously with key focus on noninvasive investigations like genetic testing if available.
4. Molecular diagnostic testing remains the mainstay for diagnosis in children suspected with SMA, Duchenne muscular atrophy, congenital myotonic dystrophy and other pediatric neuromuscular diseases.
5. Role of NCV and EMG is limited to differentiating site of lesion (nerve, muscle, neuromuscular junction), to diagnose myotonia and to ascertain the type of neuropathy (axonal or demyelinating).
6. Majority of congenital myopathies and other types of muscular dystrophies require muscle biopsy with immunohistochemistry and electron microscopy for confirmed diagnosis.
7. Consider the newer emerging investigations like skin biopsy, muscle MRI and muscle ultrasonography when indicated.

Chapter 43.2
Floppy Infant
Anaita Udwadia-Hegde, Shilpa Kulkarni

The term *floppy infant* indicates multiple disorders with various degrees of hypotonia which can be axial, appendicular or both. For the same reason it is helpful to divide the localization into two broad groups: (1) the supraspinal conditions (including the brain, brainstem and cervical spinal junction) that can be called *central hypotonia* and the segmental conditions, which are more appropriately called *motor unit hypotonia* (including anterior horn cell, peripheral nerve, neuromuscular junction and muscle). The physician must also ascertain whether the delay, when present, is just a motor delay or motor and cognitive delay together. The differential diagnosis is vast and includes a number of disorders ranging from benign conditions with good prognosis to life-threatening disorders that are incompatible with life. A systematic approach is essential for diagnosis in order to avoid unnecessary investigations.

Floppiness can be secondary to hypotonia, weakness and ligamentous or joint laxity. But *floppy baby* should be restricted to hypotonia only. The cerebral cortex, cerebellum, basal ganglia are all involved in supranuclear control of tone but the final pathway is through the lower motor neuron unit.

LOCALIZATION OF HYPOTONIA

Hypotonia may be central, developmental or peripheral in origin. A systematic approach to a child who has hypotonia, with emphasis on history and clinical examination is essential in localizing the problem. **Figure 1** depicts localization of the origin of hypotonia with examples.

It is important to distinguish weakness from hypotonia. While hypotonia is reduced resistance to passive movements around a joint, weakness is reduction in the maximum power that can be generated. Thus, floppy infants exhibit poor control of movements, delayed motor skills, alteration of postural control, increased range of motion of joints and abnormal stability. Weak infants always have hypotonia but hypotonic infants may not have weakness.

There are mainly two approaches to the diagnostic problem. The first is based on neuroanatomical localization, i.e., central nervous system (CNS) or peripheral nervous system involvement and their subsequent subdivisions as cerebral cortex, cerebellum in the CNS as against nerve, muscle, neuromuscular junction or anterior horn cell in the peripheral nervous system.

The second is to determine whether or not the hypotonia is associated with weakness. Hypotonia of central origin may be associated with weakness, while hypotonia with profound weakness usually suggests involvement of the lower motor neuron unit. Central causes account for 60–80% of hypotonic cases while peripheral causes account for 15–20%. Some disorders can cause both central and peripheral manifestations such as Pompe's disease.

Some clinical features common to most floppy babies regardless of the etiology or location of the abnormality are highlighted in **Table 1**.

APPROACH TO DIAGNOSIS

History Taking

History regarding pregnancy and neonatal period These include consanguinity, previous fetal losses, low fetal kick count and
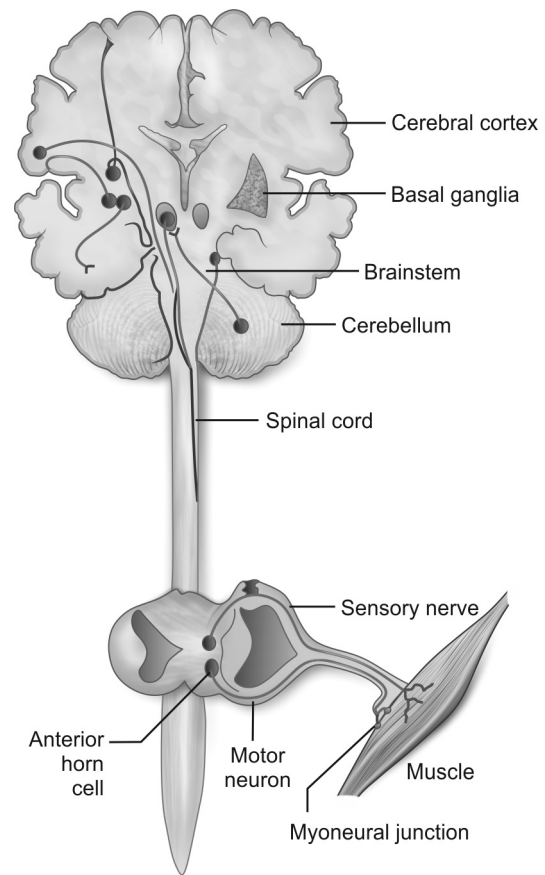
Figure 1 Localization of the origin of hypotonia
1. Cerebral cortex   2. Basal ganglia   3. Brainstem   4. Cerebellum
5. Spinal cord   6. Anterior horn cell   7. Myoneural junction
8. Muscle

Table 1 Clinical features of a floppy infant

Frog-like posture	Poor quality of spontaneous movements with legs fully abducted and arms lying by the side of body either flexed or extended
Pull to sit	Excessive head lag and rounded back
Vertical/Axillary suspension testing	Minimal support with a sensation of *slipping through the hands*
Ventral suspension	Inverted U position/ragged doll posture
Drooling and oropharyngeal pooling of secretions	Poor swallowing ability
Weak cry	Respiratory weakness
Paradoxical breathing pattern	Intercostal muscles paralysis usually with intact diaphragm
Inefficient cough	Intercostal muscles weakness
Plagiocephaly, flat occiput, arthrogryposis, and other congenital anomalies like dislocation of hip, CTEV	Decreased fetal movements
Signs of impairment in level of consciousness, feeding difficulties, seizures, apneas, abnormal posturing, abnormalities of ocular movements and of brain-stem reflexes	Features suggestive of severe CNS abnormalities and a sick floppy infant

quality of fetal movements, polyhydramnios, prolonged labor, breech presentations and emergency cesarean sections. History in the newly born of respiratory difficulties in the recovery room, need for resuscitation or ventilation problems in early infancy, infantile hypotonia, weak cry and poor feeding. Also newborn clues include any history of umbilical hernias, congenital talipes equinovarus, joint dislocations, contractures and arthrogryposis.

A detailed feeding history from birth may provide valuable diagnostic clues. Several genetic disorders may present with hypotonia, including Prader-Willi syndrome, which in later childhood shows hypotonia, obesity, mental retardation and hypogonadism but is characterized in infancy by feeding difficulties and failure to thrive. A diagnosis of infantile botulism may be prompted by a history of honey or corn syrup consumption; contamination of these products with *Clostridium botulinum* may account for significant amount of botulism cases during infancy.

Getting family details and a pedigree chart are imperative to diagnosis so as to assist with future genetic counseling.

History regarding onset, duration and progress of the weakness Acute onset (days to weeks) or chronic (months to years). Whether episodic? Is the weakness getting worse, staying the same, or getting better? Ascertain the rate of progression (days, weeks, months, or years).

Detailed history of the child's acquisition of developmental milestones Ascertain when the child was able to control his or her head, sit independently, crawl, stand with and without support, walk with and without support, gain fine pincer grasp and acquire bimanual skills (bringing objects to midline and transfer of objects). Obtain history regarding language acquisition and school performance.

Functional difficulties Identify factors that worsen or help the primary symptoms. Obtain history of fatigue or lack of endurance and muscle cramps or stiffness and any associated pain. Ask for ambulatory distances (it is useful to time prefixed distances walked at each visit for a prospective analysis); frequency of falls; transition from the floor to standing; problems in ascending and descending stairs; problems in dressing; problems reaching above the head; difficulty lifting; running ability; problems in physical education and recreational or athletic performance.

Systemic symptoms History of recent illnesses (e.g., recent viral illnesses, respiratory difficulties, pneumonia, pulmonary infections); cardiac symptoms (dizziness, syncope, chest pain, orthopnea, cardiac complaints with exertion); pulmonary symptoms (breathing difficulties, sleep disturbance, morning headaches); anesthetic history (e.g., malignant hyperthermia).

It is important to distinguish between congenital and acquired hypotonia from the history. For example, a child who becomes floppy on day 3–5 of life may be due to an inborn error of metabolism. **Table 2** summarizes a few historical clues to differentiate origin of weakness.

Physical Examination

General appearance A head-to-toe detailed general physical examination is required to assess for potentially associated organ dysfunction and to recognize existing syndromes. Dysmorphic features sharply increase the likelihood of CNS dysfunction as an explanation for hypotonia, although a long, narrow face may indicate muscle weakness (**Fig. 2**: Myopathic facies). Anterior horn

Table 2 Historical clues to differentiate origin of hypotonia

Historical clues suggestive of hypotonia of central origin	Historical clues suggestive of hypotonia of peripheral origin
• Social and cognitive impairment in addition to motor delay • Failure of visual tracking or failure to imitate facial gestures, appears lethargic • Dysmorphic features implying a syndrome or other organ malformations sometimes implying a syndrome • Features that may suggest an underlying spinal dysraphism • History suggestive of hypoxic-ischemic encephalopathy, birth trauma • Hypoglycemia and other metabolic disturbances • Seizures, depressed level of consciousness, abnormal eye movements, irregular/exaggerated breathing pattern	• Delay in motor milestones with relative normality of social and cognitive development (however, features of central nervous system involvement like dysmorphism, impaired vision and hearing, seizures and cognitive impairment can be seen in syndromic congenital muscular dystrophy) • Family history of neuromuscular disorders/ maternal myotonia

Figure 2 Typical myopathic facies

cell disease usually spares extraocular muscles, while diseases of the neuromuscular junction may be characterized by ptosis and extraocular muscle weakness. Attention to the quality of the cry is pivotal because a high-pitched or shrill cry suggests a CNS pathology, a weak cry may reflect diaphragmatic weakness and a fatigable cry may suggest a congenital myasthenic syndrome.

Physical examination of the parents This provides important diagnostic information, especially as a parent may have very mild symptoms of a serious disorder. For example, transitory neonatal

myasthenia may be suspected if the mother displays fatigability of the eyelids with upward gaze or fatigability of the arms with sustained forward extension. Infants with congenital myotonic dystrophy have severe hypotonia but their mothers are typically only mildly affected and unaware of their disorder. Mothers with myotonic dystrophy may show grip myotonia, percussion myotonia, ptosis and/or distal weakness that they were unaware of.

Systemic examination Abnormalities of other organs such as the heart or liver are more likely to be associated with a number of metabolic diseases. In the presence of hypotonia, signs of cardiac failure suggest muscle or mitochondrial disease. Hepatosplenomegaly suggests a lysosomal or glycogen storage disease. Renal cysts, high forehead, wide fontanelles are suggestive of Zellweger syndrome. Hepatomegaly and retinitis pigmentosa is seen in neonatal adrenoleukodystrophy. Congenital cataracts and glaucoma is seen in oculocerebrorenal (Lowe) syndrome. Abnormal odors are suggestive of various metabolic disorders.

Neurological assessment The clinician should review the child's posture, head shape, size and spontaneous movements along with assessment of the higher functions and cognition. In assessing tone, the child should be alert but not crying. Extremity tone is readily assessed by passive movements. Floppy infants often lie with their limbs abducted and extended along with plagiocephaly, due to the head on one side. The techniques to help elicit abnormal tone are discussed here and shown in **Figures 3A to C**.

- *Pull to sit (traction)* The infant is pulled by the arms from supine to sitting—wherein there is severe head lag with a rounded back suggestive of poor axial tone.
- *Ventral suspension* The infant is suspended in the prone position with examiner's palm underneath his abdomen and chest—the head, legs and arms flop limply by the side in an inverted U shape.
- *Vertical suspension* The infant is held under his arms in the vertical position by the examiner's finger and tends to *slip through*.
- *Scarf sign* is performed by grasping the supine infant's hand and pulling it across the chest as far as it will go without significant resistance. Normally, the elbow can be brought to the midline of the baby's chin and chest. In the hypotonic infant, the elbow can easily be brought well beyond the midline before encountering resistance. This test measures the appendicular tone in the shoulder and is sensitive to the gestational age of the infant, the degree of laxity of the ligaments and the state of alertness of the child.
- *Prone position* The infant looks flopped out in a typical frog-like posture with inability to come up and bear weight on the upper limbs and face turned to one side.

Table 3 depicts localization of disorders producing hypotonia. The deep tendon reflexes are likely the most valuable aspect of the physical examination. Brisk reflexes or clonus indicate CNS dysfunction, while diminished or absent reflexes point strongly to disorders of the lower motor unit.

Other features, which may be noted are poor axial tone, poor balance, delay in weight bearing, decreased resistance to flexion and extension, abnormal stability, truncal sway, W sitting, wide-based gait, genu recurvatum and hyperextensible joints.

Boxes 1 and 2 highlight some features associated with central and peripheral causes of hypotonia, respectively.
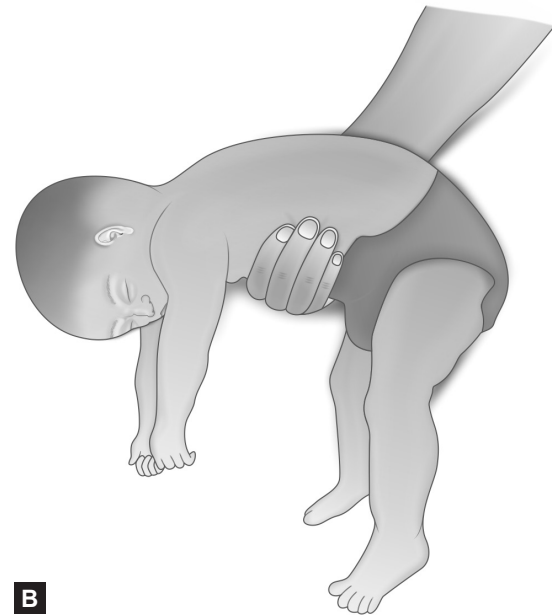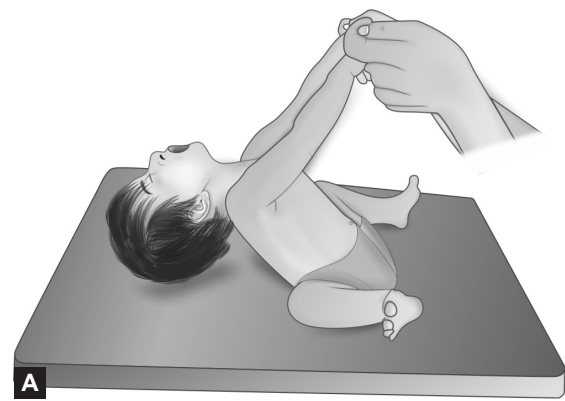
Figures 3A to C Examination techniques to elicit floppiness. (A) Pull to sit demonstrating severe head lag; (B) Ventral suspension demonstrating inverted U shape; (C) Vertical suspension demonstrating the infant tending to *slipping through*

Table 3 Localization of disorders producing hypotonia

Examination	Central causes		Anterior horn cell	Peripheral nerve	Neuromuscular junction	Muscle
	Damage/ Ongoing injury	Static (Developmental/ Genetic)				
Cognition	Impaired	Impaired	Normal	Normal	Normal	Normal/Impaired
Tone	Low evolving to high	Low	Low	Low	Low or normal	Low
Proximal vs distal weakness	> or =	> or =	> or =	<	=	>
Extent of weakness	Face – Arms + Legs +	Face – Arms + Legs +	Face ± Arms ++++ Legs ++++	Face – Arms ++ Legs +++	Face +++ Arms ++ Legs ++	Face ± Arms ++ Legs +++
Strength	N/Slight weakness	N/Slight weakness	Very weak	Weak	Weak	Weak
Muscle mass	N/Disuse atrophy	Normal	Prominent atrophy	Distal atrophy	N/decreased	Proximal atrophy/ hypertrophy
Deep tendon reflexes	N/Increased	N	Absent	Absent	N/Decreased	Decreased to absent
Babinski sign	Extensor/Flexor	Flexor	Flexor	Flexor	Flexor	Flexor
Muscle fasciculations	Absent	Absent	Present	Absent	Absent	Absent
Neonatal reflexes	Persistent	Persistent/Absent	Absent	Absent	Absent	Absent
Sensations	N	N	N	Increased/ Decreased	N	N
Seizures	±	±	–	–	–	±
Eye/Ptosis	±	±	–	–	+	±
Dysmorphisms	–	++	–	–	–	±

Abbreviations: N, normal; +, present; –, absent; >, more than; =, equals

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BOX 1 Clinical features suggestive of hypotonia of central origin

- Predominantly axial weakness
- Fisting of hands
- Normal strength with hypotonia
- Normal or brisk deep tendon reflexes, persistent neonatal reflexes
- Pseudobulbar palsy, brisk jaw jerk, crossed adductor/scissoring on vertical suspension.

BOX 2 Clinical features suggestive of hypotonia of peripheral origin

- Reduced or absent spontaneous antigravity movements with increased range of movements
- Reduced or absent deep tendon reflexes
- Myopathic facies: Open mouth with tented upper lip, poor lip seal, lack of facial expression, ptosis/restricted ocular movements
- Frog-leg posture
- Fasciculations (diagnostic of anterior horn cell disease)
- Muscle atrophy/pseudohypertrophy
- Presence of respiratory and feeding impairment.

DIFFERENTIAL DIAGNOSIS

There are a host of conditions associated with infantile hypotonia. **Table 4** lists the different conditions in two broad categories namely central and peripheral causes of hypotonia. The differentiation whether the hypotonia is static or progressive, helps in deciding if we are looking at a neurodegenerative disorder. Also differentiating into the hypotonic infant whether is a sick or a well-floppy infant is useful. Genetic disorders, e.g., Down's syndrome children are well looking and hence categorize into the well-floppy infant group. On the other hand, all the causes of acute encephalopathies

presenting with floppiness are usually sick children with a sinister prognosis.

Differential diagnosis of hypotonia in neonatal and infancy period is summarized in **Table 4**. There are certain conditions where both central and peripheral hypotonia may coexist **(Box 3)**. In most studies, central causes account for 60–80% of hypotonia cases and peripheral causes occur in 15–20%.

Most common central cause of hypotonia in early infancy is hypoxic-ischemic encephalopathy (HIE) followed by malformations. A large percentage is due to genetic or syndromic conditions of which Down's syndrome is the most common. Not many studies have been done in India and quoting one study evaluating the clinical profile of paralytic floppy infants found that spinal muscular atrophy was the most common peripheral cause of floppy children (60%) followed by congenital myopathy, and congenital muscular dystrophy which was similar to the profile seen worldwide then.

Most genetic conditions are associated with hypotonia presenting from infancy. The common ones are Prader-Willi syndrome, Trisomy 18, Velo-cardio-facial syndrome, Williams's syndrome, Cri-du-chat syndrome, etc.

Nonsyndromic central hypotonia These patients do not have a recognizable collection of somatic dysmorphic features but still have anomalies or abnormalities of the CNS that result in hypotonia. They can be placed into two major categories based on the neuroimaging (MRI) findings:

1. *With MRI evidence of developmental abnormalities of the brain* These are most often less specific, minor anomalies and are classified as types of cerebral dysgenesis. They may

Table 4 Differential diagnosis of hypotonia in neonatal period and infancy

Central causes	Peripheral causes

• Acute encephalopathies
  – Birth trauma
  – Hypoxic-ischemic encephalopathy
  – Hypoglycemia
• Chronic encephalopathies
  – Cerebral malformations
  – Inborn errors of metabolism (Mucopolysaccharidoses, aminoacidurias, organic acidurias, lipidoses, fatty acid oxidation defects, glycogen storage diseases, Menke's disease, primary carnitine deficiency)
  – Chromosomal disorders (Prader-Willi syndrome, Trisomy 21, Trisomy 13 and 18, Cri-du-Chat syndrome, DiGeorge syndrome)
  – Genetic disorders (Familial dysautonomia, Lowe syndrome, deletion and duplications and single gene disorder)
  – Peroxisomal disorders (Neonatal adrenoleukodystrophy, Zellweger syndrome)
  – Endocrine (hypothyroidism)
  – Metabolic (rickets, renal tubular acidosis)
  – Connective tissue disorders (Ehlers-Danlos syndrome, osteogenesis imperfect, congenital ligamentous laxity, benign congenital hypotonia)
• Cerebellar disorders
• Hydrocephalus
	• Spinal muscular atrophy**
	• Paralytic poliomyelitis
	• Neuropathies
	  – Hereditary motor-sensory neuropathy
	  – Congenital hypomyelinating neuropathy
	  – Acute demyelinating polyneuropathy
	• Neuromuscular junction problems
	  – Botulism
	  – Transient neonatal myasthenia
	  – Autoimmune myasthenia
	  – Congenital myasthenic syndromes
	  – Magnesium toxicity
	  – Aminoglycoside toxicity
	  – Periodic paralysis
	• Muscular disorders
	  – Congenital myopathies (Nemaline rod myopathy, myotubular myopathies, central core disease, minicore disease, etc.)
	  – Congenital muscular dystrophies (CMD) (Walker-Warburg, Fukuyama, muscle-eye-brain disease, merosin-positive CMD, early infantile facioscapulohumeral dystrophy, etc.)
	  – Congenital myasthenic syndromes
	  – Congenital myotonic dystrophy
	  – Metabolic myopathies (Acid maltase deficiency, phosphorylase deficiency, mitochondrial myopathy)
	  – Endocrine myopathies (hypothyroidism)

**Spinal muscular atrophy—have alert inquisitive facies

BOX 3 Conditions where central and peripheral hypotonia may coexist

• Familial dysautonomia
• Hypoxic-ischemic encephalopathy
• Infantile neuroaxonal degeneration
• Lipid storage diseases
• Lysosomal disorders
• Mitochondrial disorders
• Perinatal asphyxia secondary to motor unit disease.

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or may not have delayed myelination on the MRI. These children are hypotonic though tone may improve with maturation.

2. *No obvious evidence of cerebral dysgenesis* Some of these infants will be delayed in the development/maturation of myelin. Clinically, the children with delayed myelination fall into two broad groups. One group has hypotonia with motor delay and normal language and social skills. They tend to slowly catch up with their peers and although will have some deficit in motor coordination. The second group is globally delayed. They do

not usually catch up in motor and cognitive skills and have difficulties if they are expected to function in a normal school setting. Children with central hypotonia without any cerebral dysgenesis and delayed myelination can also be divided into two groups just as those with delayed myelination with a similar prognosis.

INVESTIGATIONS

Once localization to central or peripheral cause is decided, then further investigations can be planned. In case of *central hypotonia*, depending on the case, the choice of investigation is neuroimaging—for which MRI is distinctly preferred. Portable ultrasound may be used for acute management especially in the intensive care setting. Karyotype, fluorescence in situ hybridization (FISH), microarray or specific genetic tests, metabolic screening and endocrine testing may also be processed. The metabolic screening should include thyroid function studies in all hypotonic infants as hypothyroidism is one of the common and treatable causes of floppy infant.

If peripheral causes are suspected, first investigation would be creatine phosphokinase (CPK) followed by electrophysiology such as electromyography (EMG), nerve conduction study (NCS) and repetitive nerve stimulation. EMG studies are used as an important diagnostic tool to differentiate whether the disorder is myopathic, neuropathic or a denervating process. It is also helpful to decide central and peripheral causes of hypotonia. Muscle and nerve biopsy is the gold standard for structural myopathies and peripheral neuropathies. Areflexia, decreased limb movements, fasciculations detected clinically and denervation on EMG should prompt investigation straightway for anterior horn cell disorders (spinal muscular atrophy), which can be confirmed by testing for the homozygous deletion of exon 7 in the telomeric survival motor neuron gene. The diagnosis of congenital myotonic dystrophy is confirmed by testing for the expanded cytosine-thymine-guanine (CTG) trinucleotide repeat sequence on chromosome 19q13.2–q13.3. Failure to find electrophysiological abnormalities should prompt the clinician to suspect the diagnosis of Prader-Willi syndrome. The diagnosis of congenital myasthenic syndromes allows for DNA testing in some of the common syndromes. Some congenital muscular dystrophies are associated with brain abnormalities, thus neuroimaging may be required in these patients. **Table 5** serves as a guide in planning the investigations for floppy infants. **Flow chart 1** depicts an overview of evaluation for a floppy infant.

TREATMENT

Treatment of the infant who has hypotonia must be tailored to the specific condition. In general, therapy is supportive. Few conditions have specific treatment. These include hypothyroidism (thyroxine), some types of congenital myasthenic syndromes (pyridostigmine or neostigmine) and rickets (vitamin D). Some metabolic disorders may respond to specific dietary modifications or enzyme replacement therapies. Rehabilitation is an important aspect with aid of physical and occupational therapists. Nutrition is of primary importance, often achieved through nasogastric or percutaneous gastrostomy tubes for additional caloric supplementation. It also is important to maximize muscle function and minimize secondary crippling anatomic deformities. Prenatal diagnosis using amniocentesis or chorionic villus sampling is often feasible if a definitive diagnosis has been reached in the index case.

Flow chart 1 Investigation scheme for evaluation of floppy infant

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                        ┌──────────────────┐
                        │   Floppy infant  │
                        └──────────────────┘
                                 │
                                 ▼
                    ┌──────────────────────────┐
            ┌───────│ History and examination  │───────┐
            │       └──────────────────────────┘       │
            ▼                                           ▼
   ┌──────────────────┐                      ┌──────────────────┐
   │  Central causes  │                      │ Peripheral causes│
   └──────────────────┘                      └──────────────────┘
            │                                           │
            ▼                                           ▼
   ┌──────────────────┐                      ┌──────────────────┐
   │ Cerebral injury/ │                      │   Motor neuron   │
   │   Dysgenesis     │                      └──────────────────┘
   └──────────────────┘                                │
            │                                           ▼
            ▼
```

Cerebral injury/Dysgenesis

• MRI Brain
• EEG
• Infection screen (CSF, Blood)
• Ophthalmology examination

Genetic causes

• Karyotyping
• FISH analysis
• Methylation studies
• CGH Array

 Inborn errors of metabolism

• Toxic encephalopathies
   Plasma ammonia
   Amino acids (Blood, Urine)
   Urine organic acids
   Blood acylcarnitine profile
   Plasma uric acid
   Urinary sulfites
   Enzyme assays in skin fibroblasts

• Mitochondrial
   Plasma lactate, DNA depletion studies
   Respiratory chain analysis (Muscle)
   DNA based mutation analysis

• Lysosomal, e.g., Pompe's disease
   Lysosomal enzyme assay in WBC,
   Skin biopsy examination for inclusions,
   Skin fibroblast cultures plus enzyme assays
   ECG, Electrocardiography

• Perioxisomal disorders, e.g., Zellweger's
   syndrome, phytanic acid, plasma VLCFA

• Congenital disorders of glycosylation
   Isoimmune electrophoresis for transferrin

Endocrine

• Thyroid function tests

Motor neuron

• CPK Levels
• EMG/NCV
• Genetic analysis—SMN gene analysis

Nerve

• EMG/NCV
• Nerve biopsy
• Genetic mutation analysis

Neuromuscular junction

• EMG/NCV with repetitive stimulation
• Acetylcholinesterase antibodies
• Genetic analysis

Muscle

• Muscle enzyme studies
  (CPK, Aldolase, LDH)
• Muscle biopsy
• Genetic mutation studies

Abbreviations: MRI, magnetic resonance imaging; CPK, creatine phosphokinase; EEG, electroencephalography; EMG, electromyography; NCV, nerve conduction velocity; CSF, cerebrospinal fluid; SMN, survivor motor neuron; VLCFA, very long-chain fatty acid; LDH, lactate dehydrogenase.

Table 5 Clinical clues and investigations in floppy infants

Condition	Clinical clues	Investigations
Spinal cord transection or syringomyelia or other forms of spinal dysraphism	• Hemangioma or tuft of hair in midline disease • Scoliosis • Evidence of bladder or bowel dysfunction • Mixed deep tendon reflexes with absent abdominal and anal reflexes	• MRI spinal cord
Spinal muscular atrophy	• Tongue atrophy and fasciculations • Severe proximal muscle weakness with absent tendon reflexes • Preserved social interaction	• *EMG/NCV*: Anterior horn cell involvement • Deletion of the survival motor neuron (*SMN*) gene by PCR testing
Peripheral neuropathy	• Weakness predominantly distal • In most cases absent deep tendon reflexes studies • Pes cavus	• Motor nerve conduction studies • Sural nerve biopsy • Molecular DNA testing is available for specific demyelinating disorders
Myasthenia gravis	• Greater involvement of oculomotor and bulbar muscles • True congenital myasthenia due to receptor defects is rare • Exclude transient neonatal form from maternal history	• Response to acetylcholinesterase inhibitors • Single-fiber EMG • Serum antibodies to acetylcholine receptors • Electrodiagnostic studies not universally positive in young patients
Infantile botulism	• Acute onset descending weakness, cranial neuropathies, ptosis, stool culture unreactive pupils, dysphagia, constipation	• Isolation of organism from stool culture • Presence of toxin in the stool
Congenital muscular dystrophy	• Hypotonia, weakness and contractures • Associated brain and eye problems • Brain MRI for structural and white matter abnormalities	• Creatine kinase usually elevated • *Muscle biopsy*: Merosin stain
Congenital myotonic dystrophy	• Polyhydramnios with reduced fetal movements • Inverted V-appearance of the mouth • Examination of mother's face shows inability to bury her eyelashes and grip myotonia • Premature cataract surgery in the mother • Slender stature	• Molecular DNA testing by determining number of CTG repeats (normal range 5–39 repeats) • EMG of the mother
Congenital structural myopathy	• Hypotonia with feeding problems at birth • Weakness that is often nonprogressive *Nemaline myopathy*: Often associated with feeding problems *Central core*: Most often associated with malignant hyperthermia *Myotubular myopathy*: Ptosis and extraocular palsies consistent clinical features	• CK and EMG usually not helpful • Muscle biopsy is critical for definitive diagnosis • ECG • Genetic mutation studies
Glycogen-storage disease Pompe's disease	• Enlarged heart in a very floppy weak newborn • Unexplained cardiac failure • Tongue may appear large	• Blood smear vacuolated lymphocytes • Urine oligosaccharides • Typical ECG and ECHO changes • Acid maltase assay in cultured fibroblasts • Muscle biopsy usually not necessary

Abbreviations: EMG, electromyography; NCV, nerve conduction velocity; PCR, polymerase chain reaction; CTG, cytosine thymine guanine; CK, creatine kinase.

IN A NUTSHELL

1. Floppy infant is suggestive of hypotonia.
2. Hypotonia is not synonymous with weakness.
3. Hypotonia can be of central (damage, dysgenesis, genetic, metabolic) or peripheral (anterior horn cell, peripheral nerve, neuromuscular junction, muscle) in etiology.
4. History and examination are the keys to deciphering the cause of the hypotonia.
5. Investigations should be tailored to the suspected cause.
6. Central causes are most common with HIE still the most common single cause followed by genetic syndromes.

MORE ON THIS TOPIC

Bodensteiner JB. The evaluation of the hypotonic infant. Semin Pediatr Neurol. 2008;15:10-20.

Crawford TO. Clinical evaluation of the floppy infant. Pediatr Ann. 1992;21:348-54.

Gay CT, Bodensteiner JB. The floppy infant: recent advances in the understanding of disorders affecting the neuromuscular junction. Neurol Clin. 1990;8:715-25.

Johnston HM. The floppy weak infant revisited. Brain Dev. 2003;25:155-8.

Myers GJ. Understanding the floppy baby. Adv Neurol. 1977;17:295-315.

Prasad AN, Prasad C. Genetic evaluation of the floppy infant. Semin Fetal Neonatal Med. 2011;16:99-108.

Zellweger H. The floppy infant: a practical approach. Helv Paediatr Acta. 1983;38:301-6.

Chapter 43.3
Acute Flaccid Paralysis
Biswaroop Chakrabarty, Sheffali Gulati

Acute flaccid paralysis (AFP) is defined by a clinical syndrome characterized by rapid onset of weakness which at times is accompanied by bulbar and respiratory muscle weakness. The term *flaccid* indicates that the affected patient is hypotonic. Epidemiologically these cases are relevant in view of surveillance for poliomyelitis. There is no fixed duration cited in literature for rapidity of evolution and progression of clinical features to nadir. It is usually mentioned in days to weeks. The most probable explanation for this is that by keeping a liberal and open-ended definition, the chance of missing out on these epidemiologically significant cases will be minimal. Moreover, it is crucial to identify all these cases at the earliest as many of them respond dramatically to immunotherapy and delay in diagnosis and treatment may lead to significant morbidity and mortality.

BACKGROUND AND PUBLIC HEALTH IMPORTANCE

In 1988, World Health Organization (WHO) resolved for global eradication of poliomyelitis by the end of 20th century. AFP surveillance is a key strategy in that endeavor, which is a sensitive instrument for detecting poliovirus infection. From the perspective of global polio eradication initiative, AFP is defined as a case of AFP in children less than 15 years of age or paralytic illness in a patient of any age when polio is suspected. Reporting of all AFP cases less than 15 years of age is mandatory in India. All AFP cases should be investigated within 48 hours of reporting. Two stool samples should be collected from such cases at 24–48 hours apart intervals, transported and then processed at WHO accredited laboratories for virus isolation. These cases should be followed up to 60 days for any residual paralysis. The sensitivity of AFP reporting is determined by the proportion of cases with two stool samples collected within 2 weeks after onset of paralysis (ideally > 80%) and by reporting of nonpolio AFP cases in children less than 15 years of age (at least 1/1,00,000 children in 1 year). *The National Polio Surveillance Project* was started in 1997 in India. India has been declared polio free in January 2014 (last case reported 13th January 2011).

ETIOLOGY

The causes of AFP vary according to age and geographic location of patients. Anatomical localization to specific parts of the nervous system underlies the pathophysiology in distinct clinical entities. The various areas implicated in nervous system include anterior horn cell, peripheral nerves and radicles, spinal cord, neuromuscular junction and muscle. The various causes implicated in AFP according to various anatomical sites are outlined in **Table 1**.

INITIAL APPROACH TO A CHILD WITH AFP

A child with AFP is a medical emergency. The key steps in initial management are as follows:
- *Respiratory care* It is essential to check for respiratory involvement in the form of rapid breathing, shallow or

Table 1 Anatomical localization and etiological agents in acute flaccid paralysis

Anatomical site	Etiology
Anterior horn cell	Poliovirus, nonpolio enterovirus, Japanese B encephalitis
Dorsal root ganglia	Herpes simplex virus, cytomegalovirus, rabies
Spinal cord	Acute transverse myelitis, parasitic infestation (*Schistosoma*, Cysticercus, *Echinococcus*), space occupying lesions, anterior spinal artery syndrome, trauma, postcardiovascular surgery vascular complications
Radicles and peripheral nerves	Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, HIV infection per se or associated opportunistic infections or complications (herpes simplex virus, cytomegalovirus, Epstein-Barr virus, zoster, *Giardia lamblia*, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Treponema pallidum*), vitamin B_{12} deficiency, nucleoside antiretroviral agents, hepatitis B, diphtheria, rabies, tick bite, borreliosis, heavy metals (lead, arsenic, thallium, gold), chemotherapeutic agents (colchicine, vinca alkaloids, cisplatin), organic solvents including glue sniffing, critical illness, hypokalemic (acute symptomatic and familial) and thyrotoxicity
Neuromuscular junction	Myasthenic crisis, organophosphorus poisoning, drugs (aminoglycoside, phenytoin), botulism, Elapidae snake envenomation and critical illness
Muscle	Polymyositis, systemic lupus erythematosus, mixed connective tissue disorder, viral (HIV, nonpolio enteroviruses, human T-cell lymphotropic viruses), toxoplasmosis, Lyme's disease, trichinosis

Abbreviation: HIV, human immunodeficiency virus.

paradoxical respiratory efforts and use of accessory muscles. Early respiratory support and intubation is crucial in final outcome of these children.
- *Bulbar weakness detection and management* Patients should be monitored for pooling of secretions, ineffective or weak cough, nasal regurgitation of feeds and fluids, nasal intonation of voice and choking. Regular suctioning and nasogastric feeding should be practiced whenever indicated.
- *Managing cardiovascular instability* These patients are prone to develop cardiac rhythm disturbances. Under ideal circumstances, ECG electrodes should be attached to all AFP patients.
- *Rule out dyselectrolytemia and snake envenomation* At presentation, hypokalemia and snake bite should be ruled out as they have treatment implications.
- *Rule out spinal cord pathology* It is crucial to enquire for and rule out spinal cord disease as early decisions like immobilization of the patient, administration of corticosteroids and neurosurgical intervention can be taken.

CLINICAL ASSESSMENT

Once a patient with AFP is initially stabilized and all emergent measures are taken, a detailed clinical evaluation (history and examination) is obligatory to reach to a definite diagnosis.

Onset of paralysis Very rapid onset within hours to few days may be seen in Guillain-Barré syndrome (GBS), traumatic injection sciatic neuropathy, transverse myelitis, botulism, myasthenic crisis, viral myositis, periodic paralysis and occasionally in critical illness polyneuropathy. Onset within 2–3 weeks is seen in polio and nonpolio enteroviruses, varicella zoster virus, Japanese B encephalitis, tick bite paralysis and trichinosis. In entities like postdiphtheritic polyneuropathy, Lyme's disease and polymyositis the onset is in weeks to months whereas in rabies the onset may take months to years.

Progression of paralysis Maximum deficit at onset is seen in traumatic injection sciatic neuropathy. In polio and nonpolio enteroviruses, transverse myelitis, botulism, myasthenic crisis, periodic paralysis, viral myositis and critical illness polyneuropathy, the progression to nadir is within hours to few days. Progression up to 2–4 weeks is seen in GBS, varicella zoster virus, Japanese B encephalitis, rabies, tick bite paralysis and trichinosis. The paralysis may progress from few weeks to months in Lyme's disease and polymyositis. Classically ascending paralysis is described with GBS, rabies, varicella zoster virus and tick bite whereas descending variant is seen with botulism and diphtheria.

Topography of paralysis Asymmetric involvement is seen with polio and nonpolio enteroviruses, Japanese B encephalitis and traumatic injection sciatic neuropathy. Symmetric distribution of paralysis is seen in rabies, varicella zoster, GBS, transverse myelitis, botulism, diphtheria and tick bite paralysis. Proximal involvement more than distal is seen in polio and nonpolio enterovirus infection, Japanese B encephalitis, periodic paralysis and polymyositis, otherwise it is mostly a diffuse widespread involvement. Associated cranial neuropathy is seen in GBS (facial weakness), diphtheria (palatal and ocular palsy), botulism (ocular and bulbar palsy), tick bite paralysis (ocular palsy), Lyme's disease (facial weakness) and myasthenic crisis (ocular and bulbar palsy). Early respiratory muscle weakness is seen in periodic paralysis, critical illness polyneuropathy, high cervical myelopathy and occasionally in GBS and postdiphtheritic polyneuropathy.

Sensory features Sensory signs and symptoms (paresthesia, hypoesthesia, anesthesia) are seen in neuropathy secondary to neurotropic viruses (rabies, varicella zoster and Japanese B encephalitis), GBS, transverse myelitis (sensory level with band like sensation demarcating that level), postdiphtheritic polyneuropathy, Lyme's disease, postinjection traumatic sciatic neuropathy and critical illness polyneuropathy.

Deep tendon reflexes Areflexia is seen in diseases of anterior horn cell, peripheral nerves and radicles and in the spinal shock phase of cord diseases. However in spinal cord disorders, once a patient is out of spinal shock phase, then hyperreflexia is demonstrable below the level of lesion. Reflexes are usually preserved in neuromuscular junction disorders and myositis (may be hyporeflexic occasionally in the latter).

Bladder bowel involvement Early bladder and bowel involvement (urinary retention and constipation) is seen in transverse myelitis. Occasionally this is seen in rabies and GBS and rarely in poliomyelitis.

Fever at onset of paralysis This feature is seen with polio and nonpolio enteroviruses, other neurotropic viruses, occasionally with transverse myelitis, viral myositis, trichinosis and critical illness polyneuropathy.

Etiology specific features Trivial trauma leading to myelopathy should raise the suspicion of an underlying cervical vertebral instability. Enquiry should be made for exposure to heavy metals like lead and arsenic, animal bite and snake envenomation. Preceding prodromal illness and history of vaccination is seen in parainfectious causes like GBS and transverse myelitis. Specifically history should be taken for fever, sore throat with bull neck to rule out diphtheria, particularly in unimmunized children. History of preceding diarrhea is important particularly in the setting of hypokalemia or enteroviral infection. Exertion induced or postprandial acute onset of paralysis should raise the suspicion of periodic paralysis. History of preceding intramuscular injection is important in the setting of polio or unilateral sciatic neuropathy.

Other systemic features Fatigable weakness showing diurnal variation or long-term fluctuation suggests underlying myasthenia. Nonspecific prodromal illness at onset is seen in poliomyelitis. Hand, foot and mouth disease is seen with nonpolio enteroviruses whereas exanthematous vesicular eruptions are seen in varicella zoster infection. Meningeal signs are seen in polio and nonpolio enteroviruses, GBS and acute transverse myelitis. Associated pain is seen in polio and nonpolio enterovirus and other neurotropic virus infection, GBS, transverse myelitis, Lyme's disease, viral myositis, polymyositis, trichinosis and critical illness polyneuropathy. Systemic manifestation secondary to autoimmune diseases and lymphoreticular malignancies can be seen in polymyositis. Abdominal pain, rash and neuropsychiatric manifestations point towards underlying porphyria. In critical illness, polyneuropathy underlying critical sickness is present like sepsis, shock or cardiorespiratory failure.

The clinical features in a child with AFP for common causes are summarized in **Table 2**.

MANAGEMENT

In most instances, a child with AFP reaches an emergency medical service. At the first contact only, the work of AFP surveillance should be initiated at the earliest. Two stool samples should be collected from such cases at 24–48 hours apart intervals, transported and then processed at WHO accredited laboratories for virus isolation. Along with this, emergency medical measures as already mentioned should be undertaken wherever and whenever indicated.

INVESTIGATIONS

It is essential to rule out potentially treatable conditions. According to the clinical scenario, in this regard, the following investigations can be done.

- Serum potassium
- Magnetic resonance imaging spine with contrast (to rule out acute transverse myelitis, traumatic, vascular or infectious pathology of the spinal cord) **(Fig. 1)**

Table 2 Summary of clinical features in a child presenting with acute flaccid paralysis

Disease	Onset	Progression	Topography	DTRs	Sensory features	Bladder and bowel involvement	Fever at onset	Systemic features	Etiological clues
Polio and nonpolio enteroviruses	2–3 weeks	Hours to few days	Asymmetric pure motor involvement with proximal > distal	–	–	Rare	+	Meningeal signs, nonspecific prodromal illness, hand, foot and mouth disease in nonpolio group	Attack precipitated by IM injection
Rabies	Months to years	2–4 weeks	Symmetric, ascending, generalized	–	+	Occasional	+	Bite mark	History of animal bite
GBS	Hours to few days	2–4 weeks	Symmetric, ascending, generalized, cranial neuropathy (commonly VIIth), occasionally early respiratory weakness	–	+	Occasional	±	Meningeal signs occasionally	Preceding prodromal illness or vaccination
ATM	Hours to few days	Hours to few days	Symmetric, generalized, respiratory involvement in high cervical lesions	Absent (in spinal shock phase), brisk below the level of lesion later	Sensory level present	Early	±	Meningeal signs occasionally	Preceding prodromal illness or vaccination
Post-traumatic sciatic neuritis	Hours to few days	Maximum deficit at onset	One limb involved	Absent in that limb	+	–	–		Preceding history of IM injection
Postdiphtheritic polyneuropathy	Weeks to months	2–4 weeks	Symmetric, descending, generalized, cranial neuropathy (commonly palatal), occasionally early respiratory weakness	–	+	±	–	Cardiomyopathy	Preceding history of fever with neck swelling (bull neck) and membranous pharyngitis
Botulism	Hours to few days	Hours to few days	Symmetric, descending, generalized, cranial neuropathy (ocular and bulbar), occasionally early respiratory weakness	–	±	–	–		
Tick bite paralysis	2–3 weeks	2–4 weeks	Symmetric, generalized, cranial neuropathy (ocular)	–	–	–	–	Bite mark	History of travel to endemic areas
Viral myositis	Hours to few days	Hours to few days	Symmetric, generalized, painful	Normal or reduced	–	–	+		Viral prodrome
Hypokalemic periodic paralysis	Hours to few days	Hours to few days	Symmetric, proximal > distal, early neck flexor and respiratory weakness	–	–	–	–		Precipitated by postprandial state or exertion
Critical illness polyneuropathy	Hours to few days	Hours to few days	Symmetric, generalized, early respiratory involvement	–	–	–	±	Underlying sepsis, shock, cardiorespiratory failure	

Abbreviations: DTRs, deep tendon reflexes; GBS, Guillain-Barré syndrome; ATM, acute transverse myelitis; –, absent; +, present; IM, intramuscular.
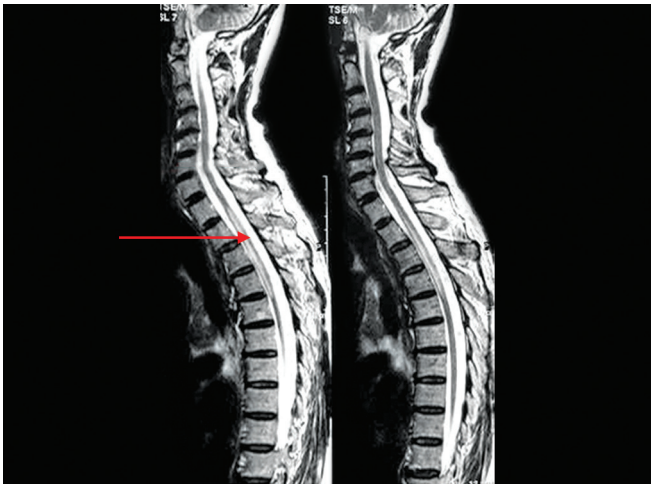
Figure 1 Magnetic resonance imaging (MRI) spine T2-weighted image shows altered signal changes (marked by red arrow) in the dorsolumbar spine characteristic of myelitis

Figure 2A Nerve conduction study showing features of demyelination (reduced conduction velocity and distal latency of motor nerve action potential)

- *Electrophysiology*: Nerve conduction study (NCS) (in suspected GBS case and also to delineate various subtypes whether demyelinating, axonal, motor, sensory or mixed) **(Figs 2A and B)**, repetitive nerve stimulation test (RNST) in suspected cases of myasthenia, NCS and electromyography in traumatic sciatic neuropathy
- Cerebrospinal fluid examination (in GBS albuminocytological dissociation is documented by the end of 1st week and beyond, if pleocytosis is present, conditions like Lyme's disease, HIV and enteroviral myelitis should be suspected)
- Serum creatine phosphokinase (in suspected cases of viral myositis)
- Urine for porphobilinogen in suspected porphyria cases
- Urine and serum toxicology screen for lead and arsenic if their toxicity is suspected
- Lyme's serology.

Apart from these treatable conditions, the above-mentioned investigations would also help to diagnose conditions which do not have definite therapy and the mainstay of treatment is supportive care. The clinical picture leading to diagnostic approach in AFP is diagrammatically depicted in **Flow chart 1**.

TREATMENT

Emergency care This has already been discussed in detail in the section, *Initial approach to a child with AFP*.

Definitive Care
This category includes treatment options which are curative.

Intravenous immunoglobulin (IVIG) Indicated in GBS and myasthenic crises (2 g/kg/day, divided over 4–5 days in once daily dosage).

Pulse methylprednisolone therapy 30 mg/kg/day (maximum: 1 g) for transverse myelitis.

Anti-snake venom in suspected cases of envenomation.

Intravenous potassium for hypokalemia.

Figure 2B Nerve conduction study showing features of axonal involvement (reduced amplitude of motor nerve action potential)

Definite treatment for porphyria and heavy metal toxicity (lead, arsenic) if clinical picture and investigations are suggestive.

Supportive Care

Prevention of bedsores Position change and air-filled mattresses should be practiced to prevent development of this complication.

Bladder and bowel care In cases of urinary retention, clean intermittent catheterization (CIC) should be practiced. In constipation, apart from nutritional modifications and laxatives, enema is indicated in refractory cases and when there are palpable fecoliths.

Nutrition Proper calorie and protein intake along with mineral and vitamin supplementation should be ensured. In case of bulbar dysfunction, patient should be put on oro- or nasogastric feeds.

Flow chart 1 Clinical features leading to investigations in a child with acute flaccid paralysis (AFP)

A child with AFP

| Sensory level, paraparesis, early bladder dysfunction | Cranial neuropathy ± respiratory and autonomic involvement ±, areflexia, sensory deficits ±, bladder involvement ± | Febrile, pure motor, asymmettic, meningismus | Preceding history of injection (usually within 24 hours), 1 limb affected no sensory deficits | Proximal weakness, pain, no sensory features, DTRs usually preserved |

Transverse myelitis

- GBS (ascending paralysis, usually VII, IX, X, XI, XII cranial neuropathy)
- Postdiphtheritic polyneuropathy (appropreate clinical setting, palatal palsy)
- Botulism (descending paralysis, ophthalmoparesism sensory ±)
- Tick bite paralysis (appropriate clinical setting, ascending, ocular involvement, no sensory deficits)
- Critical illness polyneuropathy (appropriate clinical setting, cranial neuropathy rare)
- Hypokalemic paralysis (appropriate clinical setting, early neck flexor weakness)
- myasthenia (predominant ocular and bulbar involvement, periodic fluctuation, diurnal variation)
- Rabies (ascending paralysis, autonomic instability common, appropriate clinical setting)

Nonpolio enteroviral infection

Traumatic/injection neuritis

Polymyositis, viral myositis

MRI Spine with contrast

Electrophysiology (NCS, EMG)

- Serum CPK
- Work up for underiying eltiology in polymyositis

AFP: Acute flaccid paralysis
DTR: Deep tendon reflexes
CPK: Creatine phosphokinase
EMG: Nerve conduction studies
EMG: Electromyogram
RNST: Repetitive nerve stimulation tet
CSF: Cerebrospinal fluid

- Electrophysiology (NCS, RNST)
- CSF Study

Physical and occupational therapy In the acute phase, stretching is advised to prevent development of contractures. If beyond the acute phase sequelae sets in, detailed, tailor made to individual needs, physical and occupational therapy is advised.

To conclude, AFP is both a medical and public health emergency. AFP surveillance and reporting is of paramount importance. Clinically lesions are localized to varied locations which include spinal cord, anterior horn cell, peripheral nerves, neuromuscular junction and muscles. Any child presenting with AFP should have respiratory, cardiac and bulbar involvement ruled out. It is imperative to rule out potentially treatable conditions at the earliest.

MORE ON THIS TOPIC

Marx A, Glass JD, Sutter RW. Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance. Epidemiol Rev. 2000;22:298-316.
Singhi SC, Sankhyan N, Shah R, Singhi P. Approach to a child with acute flaccid paralysis. Indian J Pediatr. 2012;79:1351-7.

IN A NUTSHELL

1. Acute flaccid paralysis is defined by a clinical syndrome characterized by rapid onset of weakness occasionally accompanied by bulbar and respiratory muscle weakness.
2. Acute flaccid paralysis surveillance and reporting is of significant epidemiological significance, particularly because of its relevance in poliomyelitis surveillance.
3. The causes of AFP vary according to the age and geographical location of the patient and anatomical localization of the lesion.
4. Initial stabilization of an AFP patient is crucial. Respiratory, cardiac and bulbar dysfunction should be ruled out immediately.
5. Potentially treatable conditions like GBS, transverse myelitis, myasthenia, porphyria, heavy metal toxicity, dyselectrolytemia and snake envenomation should be ruled out at the earliest.
6. A detailed history and clinical examination can provide clues to the underlying etiology in most of the cases.
7. Apart from emergency and definitive care, supportive care is of utmost importance as a determinant of outcome in these children.

Chapter 43.4
Guillain-Barré Syndrome
Vrajesh Udani

Landry first described the clinical picture in 1856 and in 1916 Guillain-Barré and Strohl described the cerebrospinal fluid (CSF) albumino-cytological dissociation and the delayed/absent tendon reflexes characteristic of the disease. Similarities to the inflammatory demyelinating changes seen in animal experimental allergic neuritis was reported by Asbury and co-workers in 1969. In the 1990s, it was realized that Guillain-Barré syndrome (GBS) has more types than the typical demyelinating neuropathy, when acute motor axonal neuropathy (AMAN) was described from China. In the new millenium anti-ganglioside antibodies were discovered associated with different variants of GBS (see below).

EPIDEMIOLOGY

Guillain-Barré syndrome has emerged as the major cause of acute flaccid paralysis (AFP) after the worldwide decline of poliomyelitis. The incidence in less than 18 years is 0.34–1.34 cases/100,000/year which is about half of that in adults. The average age is 4–8 years and is rare below the age of 2 years. Males appear more susceptible in all GBS variants. There are two major types—(1) the AMAN variety which often has seasonal peaks and (2) the acute inflammatory demyelinating polyneuropathy (AIDP) which appears to lack this seasonal variation.

PATHOPHYSIOLOGY

Both forms of the disease are immune mediated with involvement of both humoral and cell-mediated mechanisms. Triggers are mainly environmental pathogens like viruses—common ones noted include Epstein-Barr (EB) virus, cytomegalovirus (CMV), hepatitis A and B, varicella, enteroviruses as well as *Mycoplasma pneumoniae. Campylobacter jejuni*, a Gram negative bacteria and a leading cause of diarrhea, appears particularly important as a trigger especially in the AMAN variant **(Fig. 1)**. In one Indian study, 28% of GBS was linked to this organism probably due to poor sanitation and close contact with animals. Vaccinations like influenza, hepatitis B confer an increased risk of GBS. The recent worldwide immunization with the H1N1 vaccine in 2009 resulted in an increased incidence of 0.8 cases/million doses.

These triggers are believed to activate CD4[+] helper-inducer T-cells, which act against a variety of specific endogenous antigens, including myelin P-2, ganglioside GQ1b, GM1, and GT1a, etc. Resemblance of the triggering pathogens to antigens on peripheral nerves (i.e., molecular mimicry) leads to an overzealous autoimmune response mounted by T-lymphocytes and macrophages. Activated T-cells stimulate B-cells to produce specific antiganglioside antibodies and/or recruit macrophages as effector cells. Cytokines and chemokines released by activated T-cells or complement activation may increase capillary permeability facilitating transmigration of more macrophages and result in more myelin or axonal injury.

The location of the target antigen be it myelin or axon would decide the clinical syndrome—whether AIDP, AMAN or the Miller-Fisher syndrome (MFS). Certain antibodies are seen more frequently in some clinical syndromes, e.g., anti-GM1 and anti-GD1a antibodies in AMAN and the anti-GQ1b antibodies in MFS. However, the antigen involved in AIDP still remains unknown.

Why specific antibodies lead to specific clinical syndromes is not entirely clear but may be due to distribution and density of particular antigens, e.g., GQ1b is prominent in oculomotor nerves explaining ophthalmoplegia in MFS while GM1 is more in ventral rather than dorsal roots explaining the motor neuropathy in AMAN.

CLINICAL FEATURES

A progressive ascending symmetrical paralysis coming on over hours, days, to a few weeks is the hallmark of GBS. Pain and refusal to walk are often presenting symptoms especially in preschool children (65%) and can often lead to misdiagnosis of other non-neurologic painful conditions. Frequent radicular involvement is manifested by the positive straight leg-raising sign (SLR). Early areflexia especially the loss of ankle jerk is usual though occasionally jerks may persist especially in the AMAN variant. Bladder symptoms occur in about 10% but are usually transient.

Cranial nerve involvement typically bifacial palsy occurs in half while bulbar palsy with dysphagia, drooling and dysphonia occurs less commonly. Ophthalmoplegia is exceptional except in the Miller-Fisher variant where ataxia and areflexia form the triad. Autonomic manifestations are seen in up to one-third with dizziness, hypertension and arrhythmia.

The most dreaded complication is respiratory muscle weakness which can come on rapidly, especially in the AMAN variant and leads to the occasional mortality. About 10–15% of patients need mechanical ventilation on the whole though this number is higher in the AMAN variant.

Clinically, AMAN and ADIP could be remarkably similar though AMAN is probably more rapid in its evolution with higher grade of severity and more patients needing ventilation. MFS typically is a milder disease with full rapid recovery and will rarely be admitted to an intensive care unit (ICU). Diagnostic criteria for GBS and what makes the diagnosis of GBS doubtful is outlined in **Tables 1 and 2**, respectively.

Atypical Variants

Polyneuritis cranialis is an acute disorder with multiple cranial neuropathies usually including bilateral seventh cranial nerves with high CSF protein and slowed nerve conduction velocities (NCVs) with rapid recovery. It is associated with previous CMV infection.

Acute motor and sensory axonal neuropathy is rare and is similar to AMAN but with sensory involvement as well. The course is more severe.

A *pharyngo-cervical-brachial variant* where the paralysis involves bulbar, neck and upper limb muscles early and then may descend.

Respiratory muscle weakness may sometimes predominate initially necessitating early ventilation where the diagnosis may be at times confused with acute respiratory conditions.

Locked-in state An occasional patient may look comatose due to severe quadriplegia and pan-cranial neuropathy where a locked-in state prevents the patient from responding to any stimuli.

Acute pandysautonomia pure sensory variant Where there is predominant autonomic or sensory involvement. Both these variants are rare.

Painful variant In young children, a predominantly painful variant with minimal/no obvious weakness and preserved reflexes may lead to confusion with other medical conditions. Recovery is usually complete.
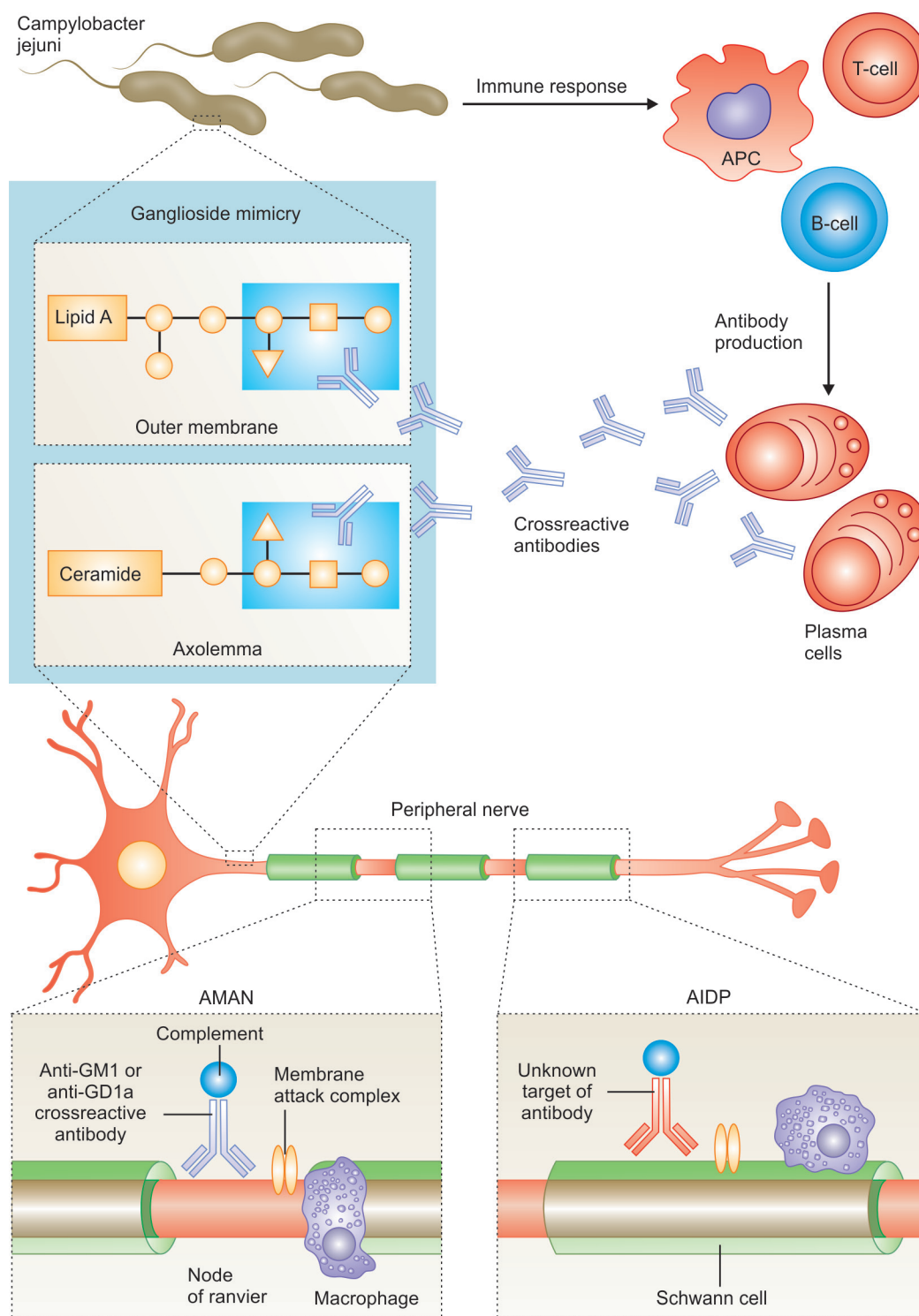
Figure 1 Immunopathogenesis of Guillain-Barré syndrome: molecular mimicry and anti-ganglioside antibodies. Infections (e.g., *Campylobacter jejuni*) can trigger humoral immune responses resulting in nerve dysfunction. Lipo-oligosaccharides on the *C. jejuni* outer membrane elicits antibodies which cross-react with gangliosides on peripheral nerves. The antigens in AMAN are located at the node of Ranvier and anti-GM1 and anti-GD1a antibodies bind to the axolemma leading to complement activation and formation of MAC leading to nerve damage. Macrophages scavenge the injured axons. In AIDP, the antigens are presumably located on the myelin sheath and induce injury to Schwann cells and myelin sheaths by a similar mechanism.

Abbreviations: AIDP, acute inflammatory demyelinating neuropathy; AMAN, acute motor axonal neuropathy; APC, antigen presenting cell; GBS, Guillian-Barré syndrome; MAC, membrane attack complex.

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Table 1 Criteria for the diagnosis of typical Guillain-Barré syndrome (GBS) (adapted from Asbury)

Features required for diagnosis
• Progressive weakness in both arms and both legs • Areflexia
Features strongly supporting diagnosis
• Progression of symptoms over days to 4 weeks • Relative symmetry of symptoms • Mild sensory symptoms or signs • Cranial nerve involvement, especially bilateral weakness of facial muscles • Recovery beginning 2–4 weeks after progression ceases • Absence of fever at onset • High concentration of protein in cerebrospinal fluid, with fewer cells than 10×10/L • Typical electrodiagnostic features • Pain (is often present).

Table 2 Features that should raise doubt about the diagnosis of GBS

• Marked persistent asymmetry of weakness
• Bladder or bowel dysfunction at onset
• Persistent bladder or bowel dysfunction
• Sharp sensory level
• Severe pulmonary dysfunction with limited limb weakness at onset
• Severe sensory signs with limited weakness at onset
• Fever at onset of neurological symptoms
• Increased number of mononuclear cells in CSF ($> 50 \times 10^6$/L)
• Polymorphonuclear cells in CSF

DIFFERENTIAL DIAGNOSIS

Nonpolio Enteroviral and Other Viral Myelitis

As poliomyelitis is now eradicated in India, *viral myelitis* is now caused mainly by nonpolio enteroviral (NPEV) and occasionally by other viruses like Japanese B encephalitis and West Nile viruses. NPEV typically have fever, pain, meningeal signs bladder involvement and asymmetric paralysis usually involving proximal lower limb muscles. *Vaccine associated paralytic poliomyelitis* may also cause a similar picture. CSF pleocytosis is usually present in the 1st week though albumin-cytologic dissociation pictures are also reported. Recovery is often incomplete. Diagnosis is by stool culture as part of government-sponsored AFP surveillance.

Around 20–30% of *rabies* victims (especially if vaccinated) present as a febrile patient with acute ascending paralysis and bladder involvement. The diagnosis becomes rapidly clear as central nervous system (CNS) involvement becomes obvious.

Acute Myasthenic Crisis and Other Neuromuscular Disorders

This occasionally can be the first manifestation of immune *myasthenia gravis* and may be confused with atypical GBS/MFS with predominant involvement of ocular, bulbar and respiratory muscles. A normal CSF, electrodecremental response on repetitive nerve stimulation and positive antiacetylcholine receptor antibody clarifies the diagnosis easily.

Botulism is the other neuromuscular-junction disorder which may be considered but it is extremely rare in our part of the world. Pupillary involvement is typical and helps to differentiate it from GBS where pupillary reflexes are normal.

Neurotoxicity of *snake-bite* involves extraocular muscles and respiratory muscles and must be considered in the differential diagnosis especially in rural regions.

Acute Transverse Myelitis

This clinical syndrome can be confused with GBS in younger children where sensory levels are difficult to ascertain. Persistent urinary retention usually helps to differentiate. Areflexia is the rule in the acute stage like in GBS. Spinal magnetic resonance imaging (MRI) helps easily differentiate the two.

Acute compressive myelopathies especially involving the conus medullaris may occasionally mimic GBS as they present with lower limb hypotonia, areflexia and pain.

Other Neuropathies

Acute intermittent porphyria should always be considered in school-age children/teenagers who present with AFP along with severe abdominal pain. Hyponatremia, hypertension and encephalopathy help to differentiate this from AMAN. Increased excretion of urinary porphobilinogens provides an answer.

Rarely in infants neuropathies associated with disorders like *metachromatic leukodystrophy* and *Leigh's syndrome* may present subacutely without obvious CNS involvement and hence get confused with GBS. Typically uniform symmetric slowing of NCV vis-à-vis the nonuniform patchy involvement in GBS suggests these diagnoses.

Acute Cerebellar Ataxia

Young children who suddenly stop walking do so due to either pain, weakness (as in GBS) or ataxia and it is sometimes difficult to differentiate these in a crying fretful toddler. Ataxia is more likely if there is no loss of antigravity movements in the supine position especially with preserved reflexes.

Antalgic Conditions

Pain and weakness often coexist in GBS. Many antalgic conditions present with inability to walk or stand unsupported and it is often difficult to differentiate whether pain or weakness is the predominant factor causing this symptom. Antalgic conditions encompass diverse disorders like synovitis, discitis, scurvy or even leukemia and must be carefully excluded if clinically suspected.

LABORATORY DIAGNOSIS

High CSF protein without a cellular response—so-called albumin-cytologic dissociation may take up to a week though changes are usually seen around 48 hours after onset. Sometimes there is a cellular response of up to 50 cells which can suggest a viral etiology. GBS associated with human immunodeficiency virus (HIV) typically has a significant CSF pleocytosis.

Nerve conduction studies peak in the 2nd week though some specific changes may be seen in the 1st week like absence of late responses, etc. Hence, the problem with both CSF and NCV is that they may be normal in the 1st week of illness. Recently spinal and sometimes cranial contrast MRI has gained popularity as changes are seen within 2 days in greater than 90% of children. Typically the ventral roots of the cauda equine show enhancement.

Antibodies to different ganglioside antigens are positive in about half of Asian/Indian patients. This positivity is more specific in AMAN and MFS. These are however not useful in early diagnosis.

TREATMENT

Plasma exchange (PE) and intravenous immunoglobulin (IVIG) have been shown to be equally effective in hastening recovery in all GBS including childhood GBS. However, the ease of administration of IVIG as well as less adverse effects makes this the first-line treatment in childhood GBS. Studies have typically involved more severely affected patients and the dosage used has been high dose 2 g/kg. Whether milder affected ambulant patients benefit from IVIG is not really studied though small studies using PE did hasten recovery in adults. Also, in a resource-poor country like ours, we need to study whether lower doses of IVIG would suffice. It is not known whether IVIG given later than 2 weeks after onset of disease would hasten recovery as all studies have used early treatment; however, treatment up to 4 weeks is common practice.

Some patients continue to deteriorate in spite of PE or IVIG. How to manage the deteriorating patient is not really known. PE followed by IVIG is not really superior to IVIG or PE alone. Whether to give PE following initial IVIG is not known. Corticosteroids have not been shown to hasten recovery and oral steroids may actually delay recovery.

Some patients have worsening after initial improvement—the so-called *treatment-related clinical fluctuation*. It is common practice to repeat IVIG. If these clinical fluctuations occur more than three times or if the recovery has not occurred 9 weeks into illness, one must consider the acute variant of chronic inflammatory demyelinating polyneuropathy (CIDP).

ICU Management

Children need transfer to ICU in the presence of any of the following: Rapidly progressive disease, bulbar dysfunction, autonomic instability, weakness of shoulder shrugging, reduction of vital capacity (VC) greater than 30% of baseline; VC less than 20 mL/kg, maximal inspiratory pressure (PI max) less than 30 cm H_2O, or maximal expiratory pressure (PE max) less than 40 cm H_2O (20/30/40 rule). PFT parameters are difficult to use because most patients do not cooperate; serial single breath counts appear more reliable and anything less than a count of 15 would be a red flag.

Generally, arterial blood gases (ABGs) are not reliable in deciding elective intubation as they tend to change late. Sleep related oxygen saturations less than 90% should be a cause for concern. Cardiac and BP monitoring is important. One should not be too aggressive in treatment of hypertension/tachycardia as sometimes dramatic reversals occur suddenly especially with beta-blockers. Thrombo-embolic complications due to prolonged immobilizations are uncommon in children but low-molecular weight heparin prophylaxis may sometimes be needed.

PROGNOSIS

In general, the outcome in children is excellent. Mortality is unusual nowadays with modern intensive care. However, in developing countries, the mortality is still reported between 11% and 13%. Though the AMAN variant reaches a more severe disability stage than AIDP and has a higher rate of respiratory failure needing ventilation, the final outcome at 12 months is excellent in both groups. MFS generally has a good prognosis and does not need immunotherapy unless it overlaps with GBS.

IN A NUTSHELL

1. Guillain-Barré syndrome has emerged as the major cause of AFP after the worldwide decline of poliomyelitis. The average age of affected children is 4–8 years.
2. There are two major types: (1) the AMAN variety which often has seasonal peaks and (2) the AIDP which appears to lack this seasonal variation.
3. Both forms of the disease are immune mediated with involvement of both humoral and cell-mediated mechanisms.
4. A progressive ascending symmetrical paralysis coming on over hours, days, to a few weeks is the hallmark of GBS.
5. High CSF protein without a cellular response—albumin-cytologic dissociation and delayed NCVs are characteristic.
6. Immunotherapy with IVIG and intensive care has made this once-dreaded disease into an eminently treatable condition with an excellent long-term outcome.

MORE ON THIS TOPIC

Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol. 1990;27:S21-4.

Dalakas MC. Pathophysiology of autoimmune polyneuropathies. Presse Med. 2013;42:e181-92.

Hughes RA, Cornblath DR. Guillian-Barré syndrome. Lancet. 2005;366: 1653-66.

Kannan MA, Jabeen SA, Mridula KR, et al. Clinical, electrophysiological subtypes and antiganglioside antibodies in childhood Guillain-Barré syndrome. Neurol India. 2011;59:727-32.

Sankhyan N, Sharma S, Konanki R, Gulati S. Childhood Guillain-Barré syndrome subtypes in northern India. J Clin Neurosci. 2014;21:427-30.

van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). Presse Med. 2013;42:e193-201.

van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol. 2008;7:939-50.

Chapter 43.5
Spinal Muscular Atrophy
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The spinal muscular atrophy (SMA) is a group of genetically determined neuromuscular disorders due to degeneration of anterior horn cells of spinal cord with or without involvement of bulbar motor neurons. Clinically they present with progressive pure lower motor neuron type of weakness characterized by symmetric proximal muscle involvement of all four limbs, wasting of muscles, fasciculations and absent deep tendon reflexes. The onset of weakness may occur at any age, from birth to adult life. Some spinal muscular atrophies show a generalized distribution of weakness, and others affect specific muscle groups. Werdnig and Hoffman independently described SMA in 1890s and the culprit gene *survival of motor neuron (SMN)* gene was identified a century later.

Various neuromuscular disorders like congenital muscular dystrophy, congenital myopathy, congenital myasthenia syndrome, congenital myotonic dystrophy and hereditary neuropathy present in a manner similar to SMA and the treating clinician should be able to differentiate them accurately as to avoid missing any treatable causes.

EPIDEMIOLOGY

The incidence of SMA is one in 6,000–10,000 livebirths and the carrier frequency is 1 in 50, which makes SMA one of the most common fatal autosomal recessive disorders. The epidemiological data from India is scanty and the findings from a hospital based observational study from eastern India showed that SMA patients constituted 20% of cases among motor neuron diseases.

ETIOLOGY

Spinal muscular atrophy results from the homozygous deletion of survival of motor neuron 1 gene (*SMN1*). There are two identical *SMN* genes present on chromosome 5q12.2–q13.3 which is designated as *SMN1* and *SMN2*. There are two copies each of *SMN1* and *SMN2* genes in normal individuals. Earlier they were termed telomeric (*SMN1*) and centromeric (*SMN2*) survival motor neuron genes. *SMN* gene codes for SMN proteins which are ubiquitously expressed and are localized in both cytoplasm and nucleus. SMN proteins are abundant in the motor neurons of the spinal cord which explains why these neurons are preferentially degenerated in SMA.

SMN1 Gene
SMN1 gene encodes *SMN1* protein, which is a 38kD polypeptide. SMN protein is a part of high molecular weight protein complex (SMN complex) which is necessary for the proper assembly of Smith class core proteins in Uridine rich small nuclear ribonuclear proteins (UsnRNP). UsnRNP are principal components of spliceosomes which execute the splicing of the pre-mRNA to produce functional mRNAs. Homozygous deletion of *SMN1* gene results in *SMN1* protein reduction and alters UsnRNP assembly and mRNA splicing. SMN may also play a key role in axonal transport in anterior horn cells.

SMN2 Gene
The coding region of *SMN2* differs from *SMN1* in a single base pair, which codes for a truncated and unstable protein. The deletion of *SMN2* alone does not produce SMA; however, the number of *SMN2* copies will determine the severity of SMA. Patients with SMA type 1 have only one copy of *SMN2*, those with intermediate SMA have two copies and those with the adult form have three or four copies of *SMN2* genes. This clearly shows that less the number of copies of *SMN2* gene, more is the severity of the disease.

CLINICAL SUBTYPES

The clinical subtypes of autosomal recessive SMA are in continuum of disease spectrum. The International SMA consortium meeting in 1992 had classified SMA into four types **(Table 1)** based on age of onset and the highest function achieved.

Spinal Muscular Atrophy Type 0
Spinal muscular atrophy type 0 (SMA0) manifests before birth, i.e., in utero as decreased fetal movement. Affected newborns have generalized weakness involving proximal more than distal muscles, hypotonia and areflexia. Newborns may have difficulty adapting to extrauterine life and experience postnatal asphyxia and encephalopathy due to significant respiratory muscle weakness. Despite intrauterine hypotonia, arthrogryposis is not present.

Spinal Muscular Atrophy Type 1 (Early Infantile Form, Werdnig-Hoffman Disease)
Spinal muscular atrophy type 1 (SMA1) is the most common which constitutes 50% of the SMA. SMA1 patients present in the neonatal period or within 6 months of life and will never attain the ability to sit independently. The disease is fatal and they usually die before 2 years of age.

These children present as floppy infants characterized by severe generalized hypotonia, proximal more than distal weakness

Table 1 International SMA Consortium classification of spinal muscular atrophy

SMA type	Genetics	Age of onset	Clinical features	Maximum function achieved	Prognosis
0 Prenatal	*SMN* gene AR	Intrauterine	Reduced fetal movements Respiratory distress at birth	Requires ventilatory support at birth	Fatal at birth
1 Infantile SMA (Werdnig-Hoffmann)	*SMN* gene AR	0–6 months	Floppy infant Bulbar and respiratory involvement	Sits with support	Death by 2 years of age
2 Intermediate SMA	*SMN* gene AR	6–18 months	Delayed motor milestones	Sit without support Unable to walk	Variable
3 Juvenile SMA (Kugelberg-Welander)	*SMN* gene AR	After 18 months	Pseudomyopathic pattern	Able to walk with assistance	Variable
4 Adult SMA	*SMN* gene AR	Usually after 30 years (Above 5 years)	Pseudomyopathic pattern/ neuropathic pattern	Able to walk independently	Slow progression Normal lifespan

Abbreviation: AR, autosomal recessive.

and areflexia. Due to severe hypotonia, infants assume *frog-leg position* while lying supine and have head lag on traction test. The *frog-leg* position occurs due to severe hypotonia and at rest baby assumes a characteristic position with the thighs externally rotated and abducted with the knees flexed. When pulled from a supine to a seated position, these children are unable to lift their heads and demonstrate severe head lag **(Fig. 1)**. Deep tendon reflexes are usually absent and the sensory examination is normal. Fingers may have polyminimyoclonus which are fine, small amplitude involuntary movements due to dense fasciculations. Bulbar motor neuron involvement results in progressive feeding difficulty, weak cry and tongue fasciculations. Extraocular movements are always normal. Intercostal muscles are severely weak, but diaphragm involvement occurs late in the disease. Respiratory distress in these children is due to intercostal muscle weakness and aspiration pneumonia. Contractures may develop after several months of immobilization. Oculofacial muscle sparing and an active alert child help the clinician to distinguish SMA from other causes of hypotonia in infants.

Cardiac abnormalities like atrial and ventricular septal defects, although uncommon has been described in severe SMA. Prognosis is bad as they usually die before 2 years of age due to respiratory failure and aspiration pneumonia.

Spinal Muscular Atrophy Type 2 (Late Infantile Form, Intermediate Form)

Spinal muscular atrophy type 2 (SMA2) patients are normal at birth and usually present to the clinicians as delayed motor milestones with normal language and social milestones. The age of onset is between 6 months and 18 months and they are able to sit unsupported with variable bulbar and respiratory involvement. Lower limb weakness is more than arm weakness and the disease progression is slower than SMA1. Most children eventually are able to roll over and sit unsupported. Some of them are able to acquire standing position but they never achieve independent walking. They have prominent hip and knee contractures, kyphoscoliosis, club feet and bilateral polyminimyoclonus. Weakness of trunk muscles produces kyphosis and scoliosis. Eventually patients become wheelchair confined. The clinical severity and prognosis vary markedly with some patients dying early because of respiratory failure and others surviving into adulthood.

Figure 1 A 7-month-old baby with spinal muscular atrophy. There is significant head lag when the baby is being pulled up by pull to sit maneuver denoting hypotonia

Spinal Muscular Atrophy Type 3 (Juvenile Form, Kugelberg-Welander Disease)

Spinal muscular atrophy type 3 (SMA3) patients are normal at birth and they manifest motor weakness after 18 months of age. Although they attain independent walking ability, they develop slowly progressive limb-girdle pattern of weakness with lower limbs more affected than upper limbs. They have difficulty in climbing stairs, getting up from squatting position and use Gower's maneuver to do so. They develop waddling gait (Trendelenburg's sign) with excessive lumbar lordosis and protuberant abdomen. Neck and truncal muscle weakness develop later. Pseudohypertrophy of the calf muscles occurs sometimes which is due to relative preservation of calf muscles as compared to thigh muscles. The clinical profile resembles limb-girdle muscular dystrophy, but the presence of wasting, fasciculations and areflexia helps to differentiate from a primary muscle disease. The fasciculations in the SMA3 are much more pronounced than in SMA1 and SMA2. SMA3 has two subtypes based on age of onset:

1. Spinal muscular atrophy type 3a (SMA3a) in whom the age of onset is between 18 months and 3 years. They have a more severe course and lose ambulation earlier when compared to spinal muscular atrophy type 3b (SMA3b).
2. Spinal muscular atrophy type 3b is designated when the age of onset is after 3 years. They have milder phenotype and are mostly ambulant with or without assistance.

Spinal Muscular Atrophy Type 4 (Adult Onset, Pseudomyopathic Type)

The adult onset SMA was earlier termed as pseudomyopathic type due to resemblance with limb-girdle muscular dystrophy. Spinal muscular atrophy type 4 (SMA4) usually occurs after 30 years of age and the clinical features are similar to intermediate type with limb-girdle pattern of involvement. The patient initially manifests with difficulty in climbing stairs or getting up from squatting position. Later they have buckling of knee due to quadriceps weakness which is often a prominent feature. Upper limb involvement occur late; bulbar, respiratory involvement and bony deformities are rare. Proximal muscles are wasted and 75% of these patients have fasciculations. Muscle cramps can occur but are not a prominent feature. There is no ophthalmoparesis or ptosis and muscle stretch reflexes are absent. They remain ambulatory for decades and majority have a normal lifespan.

Variants of SMA not due to *SMN* Gene Mutations

Some of the genetic causes of anterior horn cell are due to mutations other than *SMN* gene involvement, but they have almost similar phenotype to SMA with some atypical features **(Table 2)**. They have autosomal dominant, autosomal recessive or X-linked inheritance patterns.

Spinal muscular atrophy with congenital arthrogryposis and bone fractures Spinal muscular atrophy with congenital arthrogryposis and bone fracture is an SMA variant which manifests in utero with decreased fetal movement, multiple joint contractures and bone fractures at birth. They require ventilatory support for survival at birth.

Fazio-Londe disease Fazio-Londe disease is a rare childhood onset form of atypical SMA with autosomal dominant or autosomal recessive inheritance. The predominant muscle groups affected are facial and bulbar. The affected children are normal at birth but develop progressive bulbar palsy and eventual respiratory failure in the 2nd decade of life. There is no evidence of involvement of other motor neurons or the extraocular muscles.

Finkel type SMA Finkel type SMA is similar to typical adult onset SMA (SMA4) except for autosomal dominant inheritance pattern. This presentation is due to the heterozygous mutation in the gene encoding vesicle-associated membrane protein B (VAPB) on chromosome 20q13. The age of onset is in 3rd decade of life and these patients have proximal muscle weakness with lower limb involvement more than upper limbs. This disease is very slowly progressive and most patients remain ambulatory for decades after clinical onset.

Distal spinal muscular atrophy Distal spinal muscular atrophy (DSMA) is inherited as autosomal dominant or recessive fashion and has considerable overlap with hereditary motor neuronopathy (HMN). DSMA is classified into five types and are characterized by distal muscle weakness, wasting, and local areflexia without significant sensory involvement, with or without pes cavus, vocal cord or diaphragmatic involvement. Distal SMA were earlier termed as SMA type 5, but later found to have similar phenotype and genetic mutation as HMN.

Spinal muscular atrophy in general presents with proximal muscle weakness and wasting while the distal SMA behaves like motor neuropathy with distal muscle involvement. The distal form of SMA has a relatively better prognosis and the disease stabilizes in the later stages with patients remaining ambulant and has a normal lifespan except in DSMA1.

Distal spinal muscular atrophy type 1 is also known as spinal muscular atrophy with respiratory distress type 1 (SMARD1) and hereditary motor neuropathy type 6 (HMN6). SMARD1 is a very rare autosomal recessive motor neuron disorder that affects infants and is characterized by diaphragmatic palsy, symmetrical distal muscle weakness, muscle atrophy, peripheral sensory neuropathy, areflexia and autonomic nerve dysfunction. SMARD1 is caused by mutations in the gene for immunoglobulin mu-binding protein 2 (IGHMBP2) located on chromosome 11q13. The disease is fatal with most of the patients requiring ventilatory support and usually dying within the 1st year of life.

DIFFERENTIAL DIAGNOSIS

Congenital muscular dystrophy These children have mental retardation, seizures and dysmorphic facies. They have contractures and grossly elevated serum creatinine phosphokinase (CPK) values with magnetic resonance imaging (MRI) brain showing lissencephaly (cobble stone appearance) or white matter T2W hyperintensity.

Congenital myopathy Dysmorphic facies, ptosis, extraocular muscle paresis and cardiac involvement are seen in these children. Serum CPK and MRI brain is normal.

Congenital myasthenia syndrome These children have fluctuating or persistent weakness of ocular, bulbar, or limb muscles; or arthrogryposis in infancy.

Neonatal myasthenia gravis In 15% of infants born to mothers with autoimmune myasthenia gravis, transient myasthenia occurs in the neonatal period related to transfer of acetylcholine receptor antibodies across the placenta. Affected infants may require respiratory support temporarily and in majority of cases, the symptoms resolve within the 1st month of life.

Congenital myotonic dystrophy Approximately 25% of infants born to mothers with myotonic dystrophy present in infancy. They have facial muscle weakness, inverted V-shaped mouth and myotonia. Examination of mother and positive family history aid in the diagnosis.

Metabolic myopathy like acid maltase deficiency Deficiency of α-1,4-glucosidase patients presents with a severe skeletal myopathy, cardiomyopathy and may have encephalopathy. The diagnosis is confirmed by enzyme assay.

Peripheral neuropathy Charcot-Marie-Tooth disease type 3 (CMT3), or Dejerine-Sottas disease (DSS): DSS is a rare demyelinating neuropathy characterized by delayed motor milestone, proximal weakness, global areflexia and hypertrophied peripheral nerves. The motor nerve conduction velocities are less than 10 m/s which clinches the diagnosis.

Congenital hypomyelinating neuropathy (CHN) CHN is similar to DSS in presentation and some consider CHN to be an extreme form of DSS. Sural nerve biopsies helps to differentiate between these two entities; presence of demyelination/remyelination and an abundance of well-organized onion bulbs favor DSS and only hypomyelination is seen in CHN.

Cerebral hypotonia These children will have features of cerebral involvement like encephalopathy (irritability and poor feeding), seizures and brisk deep tendon reflexes.

DIAGNOSIS

Molecular diagnosis Homozygous *SMN1* exon 7 deletions as detected by PCR-RFLP (polymerase chain reaction—restriction fragment length polymorphism) is responsible for the disease in 94% of patients with typical SMA. If no homozygous deletion is detected then SMN copy number analysis has to be done and if two SMN copies are present, then alternate diagnosis is considered. If only one *SMN1* copy is present, small intragenic *SMN1* mutations may be responsible for the SMA **(Flow chart 1)**.

Table 2 Variants of SMA not due to *SMN* gene mutation

Variant	Genetics	Age of onset	Clinical features
SMA with congenital arthrogryposis and bone fractures	Xp11.3–q11.2	In utero	• Reduced fetal movements • Contractures and multiple bone fractures • Requires ventilatory support at birth
Spinal muscular atrophy with respiratory distress (SMARD)	Immunoglobulin mu-binding protein 2 (IGHMBP2) AR inheritance	At birth–6 months	• Respiratory distress, cardiomyopathy and lactic acidosis • Distal > proximal muscle weakness
Fazio-Londe disease	AD/AR	Childhood	• Progressive facial and bulbar palsy • Respiratory failure by 2nd decade
Brown-Vialetto-Van-Laere syndrome	Mutation in Riboflavin transporter gene	Before 18 years	• Similar to Fazio-Londe but has associated sensorineural hearing loss • Treatable with riboflavin supplementation
Kennedy's disease (X-linked recessive bulbospinal neuronopathy)	X-linked recessive CAG trinucleotide repeat sequence at androgen receptor	After 30 years	• Bulbar involvement with proximal muscle weakness, wasting and fasciculations • Gynecomastia and testicular atrophy may be present

Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

Flow chart 1 Approach to genetic analysis of SMA
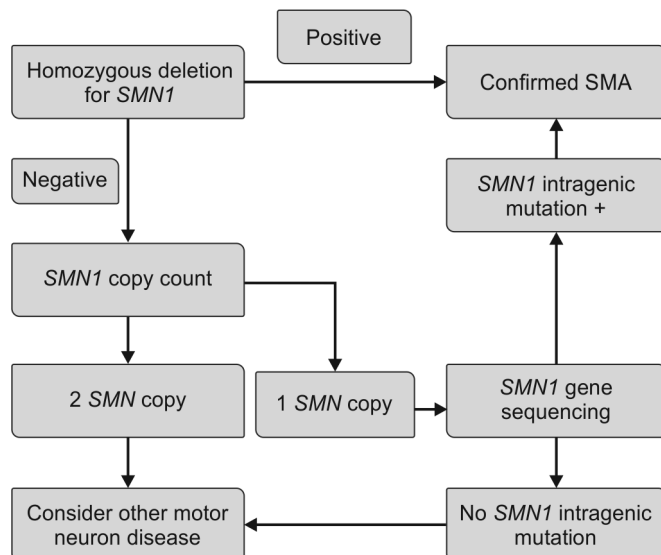
Note: If SMA is suspected, genetic analysis (homozygous deletion of *SMN1* gene) will confirm the entity and no further investigations are required. If no homozygous deletion is detected, *SMN1* copy number is ascertained and if two copies are found an alternate diagnosis is considered. If only single *SMN1* copy is present then *SMN* gene sequencing is done to rule out any intragenic mutations. If single *SMN1* copy shows intragenic mutations then SMA is confirmed and if absent then alternate diagnosis is considered. *Abbreviations:* SMA, spinal muscular atrophy; SMN, survival of motor neuron; +, present

Nerve conduction study (NCS) and electromyography (EMG) The motor NCS may be normal or the compound muscle action potential may be reduced. The sensory NCS is normal. EMG shows features of denervation like fibrillation potentials, positive waves and fasciculations. Motor unit action potentials are of large amplitude, long duration, polyphasics with reduced recruitment (neurogenic pattern).

Muscle biopsy Muscle biopsy is pursued if the genetic analysis is negative and if primary muscle disease is suspected after NCS-EMG. The muscle biopsy in SMA shows evidence of denervation atrophy. The features of denervation atrophy are as follows: Group fascicular atrophy **(Fig. 2)**; small angular atrophic muscle fibers; fiber type grouping, i.e., areas with either muscle fiber type 1 or type 2 only which is due to chronic reinnervation.
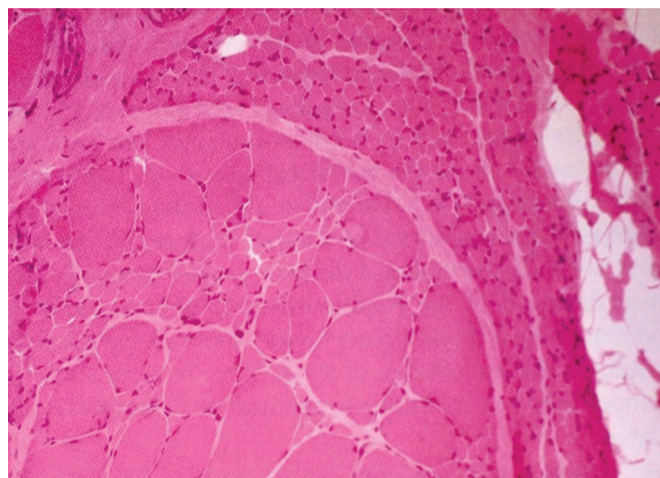
Figure 2 Hematoxylin and Eosin stain of muscle biopsy at 200X of SMA1: Group atrophy along with small angulated fibers

Serum creatinine phosphokinase (CPK) CPK is normal or 2–4 times elevated.

CLINICAL MANAGEMENT

Spinal muscular atrophy is a genetic disease for which no cure is available at present and only supportive management can be offered **(Table 3)**. Nevertheless, animal and human trials are ongoing for the identification of a cure for this fatal disease.

Family Education and Counseling

During the first meeting with parents, it is important to explain the disease process, pathogenesis, and the patient's prognosis. Other important genetic topics including sibling recurrence risk, carrier testing and information that may help with family planning (prenatal diagnosis) should be discussed with the parents. The physician should also formulate a plan of multidisciplinary intervention with the family.

Genetic Counseling

Spinal muscular atrophy has autosomal recessive inheritance pattern and the carrier state of *SMN1* gene deletion in the population is high. If a child is affected, the chance of next sibling getting affected is 25%. Proper genetic counseling should be offered to the parents and the relatives and carrier testing should be done. A prenatal diagnosis in the subsequent pregnancy is also advised.

Pulmonary Care

The key respiratory problems in SMA include impaired cough resulting in poor clearance of lower airway secretions; hypoventilation during sleep; chest wall and lung underdevelopment; recurrent aspiration and pneumonia and scoliosis. Pulmonary disease is the major cause of morbidity and

Table 3 Consensus statement for standard of care in spinal muscular atrophy

Complications	Monitor	Management
Pulmonary care		
Respiratory failure	• Arterial blood gas analysis • Chest X-ray • Oxygen saturation	• Noninvasive ventilation • Invasive ventilation if required and needs detailed discussion with the parents
Impaired cough		• Manual assisted coughing • Cough assist devices
Pooling of secretions		• Frequent suctions, chest physiotherapy and prevention of aspiration
Aspiration pneumonia	Total count and chest X-ray	• Antibiotics
Prevention of respiratory infections		• Influenza and pneumococcal vaccines
Nutritional support and hydration	Body weight	• Feeding tubes • Dietician opinion for a adequate diet • Gastrostomy/jejunostomy
Speech	Speech assessment	• Speech therapy
Neurorehabilitation		• Physical therapy • Occupational therapy • Prevention of contractures • Prevention of osteopenia and fractures
Scoliosis		• Corrected surgery • Spinal brace
Orthoses		• Walkers • Limb orthoses

mortality in SMA1 and SMA2 and may occur in a small proportion of patients with SMA3. Respiratory assessment includes evaluation of cough effectiveness, observation of breathing and monitoring gas exchange. Ventilatory support should be added at night if sleep-disordered breathing is present and cough assistance provided if cough efficiency is reduced. Polysomnography is useful even in children without obvious symptoms, and can be used to initiate and titrate respiratory support. Swallowing evaluation is indicated in cases of acute unexplained respiratory deterioration and recurring pneumonia.

Airway clearance Caregivers of these patients should learn to assist coughing in all patients with ineffective cough. These can be done manually or with mechanical cough assisted devices (mechanical insufflation-exsufflation). Daily assisted cough is recommended in more severely affected patients. Secretion mobilization techniques include chest physiotherapy, postural drainage and oral suctioning can assist in removing secretions.

Respiratory support In patients with daytime hypercapnia, respiratory support is clearly indicated. In children with sleep-disordered breathing, nocturnal noninvasive ventilation reduces symptoms of sleep disturbance, nocturnal sweating and improves quality of life. Noninvasive ventilation settings are individualized to achieve adequate inspiratory chest wall expansion, air entry and normalization of oxygen saturation. Noninvasive ventilation should be combined with airway clearance techniques. In nonsitters the option of tracheostomy and mechanical ventilation needs to be discussed with parents in consideration with the child's quality of life.

Nutritional Care

The main gastrointestinal and nutritional complications in SMA are: feeding and swallowing problem due to bulbar dysfunction; gastrointestinal dysfunction like constipation, delayed gastric emptying and gastroesophageal reflux and weight-related problems as the nonsitters have growth failure and excessive weight gain is a problem with sitters and walkers.

When delayed gastric emptying or diminished motility is present, prokinetic agents like metoclopramide or domperidone is useful. Short-term courses of H_2 receptor blockers (e.g., Ranitidine) and proton pump inhibitors (e.g., omeprazole and pantoprazole) can be given if chest discomfort is present. Placement of percutaneous gastrostomy tube is advised when significant bulbar dysfunction is present but it does not prevent aspiration. In some children with severe gastroesophageal reflux Nissen fundoplication can be done.

Supportive Management

Children with SMA should be provided routine vaccinations, appropriate nutritional support orally or via a feeding tube and proper hydration. Pneumococcal pentavalent vaccines as well as influenza vaccines are advised to prevent respiratory tract infection in these patients.

Orthopedic care and rehabilitation The key problems in rehabilitation are contracture formation, spinal deformity, skeletal pain, osteopenia and fractures. Physiotherapy includes stretching, nonfatiguing active range of motion exercise, and especially aqua therapy to improve the endurance of muscles and prevent contractures. Upright weight bearing and ambulation is also encouraged.

Occupational therapy Occupational therapist plays an important role in improving the functional skills of the disabled patient. In children with limited hand function, adaptive devices are available for power mobility control. Home modifications should be made for safe accessibility and optimal independence.

Goals of therapy and surgery depend on functional level of the child and the family's wishes. Appropriate sitting posture should be maintained and walking should be encouraged with assistive devices and orthotics. Spinal orthoses may provide postural support but do not prevent progression of scoliosis. Scoliosis surgery appears to benefit patients who survive beyond 2 years of age when curves are severe and progressive and should be performed while pulmonary function is adequate.

Newer Therapeutic Strategies

Neuroprotective strategies Several agents were used as neuroprotective drugs to rescue motor neurons; Riluzole a glutamate antagonist, creatine to improve energy metabolism, and albuterol for its anabolic properties and the molecular effect on *SMN2* gene expression has been studied without much success.

Antisense oligonucleotides (ASOs) Synthetic ASOs bind to *SMN2* derived transcripts and promote exon 7 inclusion during splicing which has resulted in increase in SMN protein levels in cell-based models.

Histone deacetylase inhibitors (HDAC) Control of the acetylation state of histones is one of several epigenetic mechanisms that regulate gene expression. Sodium butyrate was shown to increase full-length *SMN2* transcript levels and protein levels in cell lines derived from SMA patients. The half-life of this compound made it an unlikely candidate for human trials. Other HDAC inhibitors like phenyl butyrate, hydroxyurea and valproic acid are also being explored.

Gene therapy Adeno-associated virus has been used to replace *SMN1* gene in mouse models. Technical difficulties with respect to efficient gene delivery to spinal cord motor neurons and limitations in human gene therapy necessitate further studies in this area.

Stem cell therapy The use of stem cells to help maintain or restore vulnerable motor neuron populations has been explored. It is a promising endeavor as proved by an animal study with differentiated embryonic stem cells transplanted into the spinal cord of rats with motor neuron injury which resulted in the successful reinnervation of lower extremity muscles.

IN A NUTSHELL

1. Spinal muscular atrophy is an autosomal recessive disease due to homozygous deletion of *SMN1* gene in chromosome 5q.
2. Spinal muscular atrophy is due to degeneration of anterior horn cells of spinal cord with or without cranial motor nuclei.
3. Spinal muscular atrophy has been classified into four types by International consortium of SMA based on age of onset and highest function achieved. SMA0 manifests in utero as decreased fetal movement and has respiratory failure at birth. SMA1 present as floppy infant while delayed motor milestones is the presenting feature in SMA2. A limb-girdle pattern of weakness with wasting, fasciculation and areflexia is observed in SMA3 and SMA4.
4. The characteristic feature is normal intelligence, sparing of ocular and facial muscles.
5. Prognosis is grim in SMA0 and SMA1 while SMA3 and SMA4 remain ambulatory with or without support.
6. Mortality is mainly due to respiratory failure and aspiration pneumonia.
7. Spinal muscular atrophy is diagnosed clinically and confirmed by genetic analysis.
8. In SMA variants, electrophysiology and histopathology is largely relied upon for diagnosis.
9. Once the diagnosis is established parental counseling and family education is given regarding the genetics of the disease and prognosis.
10. No cure has been identified so far for SMA.

MORE ON THIS TOPIC

D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71.

Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol. 2012;11:443-52.

Prior TW. Perspectives and diagnostic considerations in spinal muscular atrophy. Genet Med. 2010;12:145-52.

Prior TW. Spinal muscular atrophy: a time for screening. Curr Opin Pediatr. 2010;22:696-702.

Singh P, Liew WK, Darras BT. Current advances in drug development in spinal muscular atrophy. Curr Opin Pediatr. 2013;25:682-8.

Viollet L, Melki J. Spinal muscular atrophies. Handb Clin Neurol. 2013;113:1395-411.

Wadman RI, Bosboom WM, van der Pol WL, et al. Drug treatment for spinal muscular atrophy types II and III. Cochrane Database Syst Rev. 2012;4:CD006282.

Wadman RI, Bosboom WM, van der Pol WL. Drug treatment for spinal muscular atrophy type I. Cochrane Database Syst Rev. 2012;4:CD006281.

Wyatt TJ, Keirstead HS. Stem cell-derived neurotrophic support for the neuromuscular junction in spinal muscular atrophy. Expert Opin Biol Ther. 2010;10:1587-94.

Zanetta C, Riboldi G, Nizzardo M, et al. Molecular, genetic and stem cell-mediated therapeutic strategies for spinal muscular atrophy (SMA). J Cell Mol Med. 2014;18:187-96.

Chapter 43.6
Muscular Dystrophies

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Muscular dystrophies are inherited progressive disorders of muscles usually caused by defects in cytoskeletal proteins or enzymes, leading to degeneration and regeneration of muscle fibers and resultant replacement by adipose and fibrous tissues. Muscular dystrophies lead to inexorably progressive muscular weakness and resultant chronic disability.

A wide variety of genetic defects lead to dystrophies. The initial clinical classifications of dystrophies took the base of clinical features like age at onset and phenotypic characteristics, along with the Mendelian genetics. **Table 1** shows one such basic approach to categorizing dystrophies. In the recent years the field has seen remarkable advancements. The emergence of investigative techniques like histopathology, enzyme histochemistry, immunocytochemistry and electron microscopy studies have greatly increase our understanding of the pathophysiology of muscular dystrophies at the cellular and molecular levels. The next leap has been molecular genetics. With advent of molecular genetics, we are able to diagnose muscular dystrophies with accuracy and have developed further understanding of the process of dystrophies. These advances have led to accurate diagnosis, antenatal diagnosis and genetic counseling, and to an extent, prevention of these progressively disabling conditions. While these advances have not yet translated into definable therapies for the sufferers, we are knocking at the doors with newer treatment. It would appear that coming times will see effective therapies for these diseases.

DUCHENNE MUSCULAR DYSTROPHY/BECKER MUSCULAR DYSTROPHY

This is the most frequent and best studied early onset muscular dystrophy. It was described as pseudohypertrophic muscular dystrophy by Gaetano Conte (1836) and Meryon (1851). It was named after Duchenne who described it in 1868.

Epidemiology

Duchenne muscular dystrophy (DMD) begins in early childhood and runs a relatively rapid, progressive course. The incidence is about 1 in 3,500 live male birth. Being an X-linked recessive trait, it is seen almost exclusively in males. But manifesting females have been documented **(Box 1)**. DMD occurs in all communities in India. Due to prevalent religious concepts and illiteracy, more than one case of dystrophinopathy in a family continues to be seen in India.

Table 1 Classification of muscular dystrophy based on mode of inheritance

X linked	Autosomal recessive	Autosomal dominant
DMD	LGMD 2 (A-O)	LGMD 1 (A-E)
BMD	MDC	MDC (Ullrich/Bethlem)
EMD	Distal myopathy (Nonaka, Miyoshi)	Distal myopathy (Walender, Udd, Laing, Markesbery-Griggs)
		FSHD

Abbreviations: DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MDC, congenital muscular dystrophy; EMD, Emery-Dreifuss muscular dystrophy; FSHD, facioscapulohumeral dystrophy.

BOX 1 DMD manifestation in female

When female patients manifest the disease, they may have only one X chromosome, as occurs in the Turner syndrome (XO), and that chromosome carries the Duchenne gene, or the Lyon principle may be operative, i.e., there is inactivation of the unaffected paternal X chromosome allowing expression of the mutated Duchenne protein from the maternal chromosome in large proportion of embryonic cells.

Etiology

Mutation on short arm of X-chromosome at Xp21 leads to DMD. It is one of the largest genes, spanning 2.5 MB (0.1% of total genome). It consists of 79 exons (0.6% of total gene) and codes for a 14kb mRNA. The gene product is dystrophin, a 428 kd protein. It is expressed in the skeletal, cardiac and smooth muscles of the body and also in the brain. The rate of spontaneous mutations is high in this large gene. Deletion or duplication of gene segments is seen in two-third of patients. Deletions are seen at two *hot spots*. Most common deleted region is between exons 43 and 52 followed by that between exons 2 and 21. Duplications are less common than deletions and further smaller number of patients has point mutations, which require elaborate and expensive genetic testing. Mutation in the DMD gene results in loss of function of dystrophin.

Koenig proposed *The reading frame rule* to explain the molecular basis of two allelic forms of muscular dystrophies DMD/ Becker muscular dystrophy (BMD). 90% of cases of DMD and BMD follow the reading frame rule. Out of frame deletions lead to DMD while in frame deletions lead to BMD **(Fig. 1)**. In the minority of patients who do not follow the frame shift rule, milder clinical phenotypes are seen particularly in exons 3 to 7.

Pathogenesis

Dystrophin is located subsarcolemally and is a cytoskeletal protein **(Fig. 2)**. Absence of dystrophin leads to delocalization of
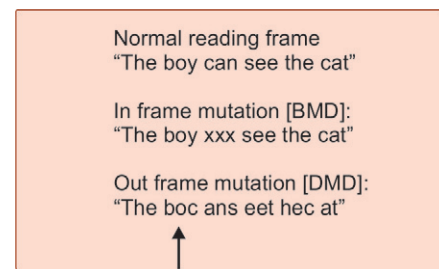
Figure 1 Reading frame rule in DMD/BMD
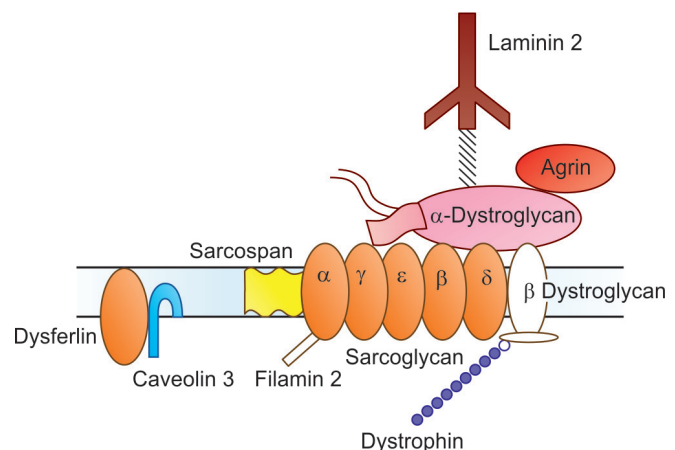
Figure 2 Dystrophin-Glycoprotein complex
Source: Dr Renuka Yadav.

dystrophin associated proteins from the membrane, disruption of the cytoskeleton with resultant membrane instability and increased susceptibility to mechanical stress. In addition, altered membrane permeability and abnormal calcium homeostasis are thought to play a role, with increased cytosolic calcium concentration leading to activation of proteases such as calpains. The absence of nitric oxide synthase, delocalized from the subsarcolemmal membrane, may contribute to dystrophic features, in indirect ways. Commonly studied animal model of DMD is mdx mouse, carrying a nonsense mutation in exon 23.

Clinical Features

Presenting Features

The most frequent presenting symptoms are motor delay or an abnormal gait. Affected boys present with difficulty in running or getting up from the ground, frequent falls, or toe-walking. Most present between 3–5 years. Less frequent presentations include language or global developmental delay, or incidentally raised serum Creatine kinase or transaminase level when these investigations are performed for other reasons.

At birth, children usually do not have any symptoms. Only occasionally, delay of motor milestones may be seen. Mothers notice clumsiness of gait which is initially taken as normal, but it persists. The problem soon becomes more clear as children begin seeking support while getting up from the ground and rise with support of one hand on the knee, the Gower's maneuver **(Figs 3A to E)**. At this stage, calf hypertrophy begins.

At 2–3 years of age, running becomes different and children cannot jump with both feet off the ground. Tightness begins at tendoachillis and may be seen in other lower limb joints as well. By 5 or 6 years of age, further weakness is noted and children have more difficulty in rising from chair and climbing stairs.

It is important to note that the natural growth spurt is at its best *between 2–6 years* of life and tends to offset the progressive muscular weakness resulting from the dystrophy. Hence, some parents report motor task improvement in children at this stage. This apparent improvement seen in some children declines as age advances.

By the age of 6 or 7 years, the weakness becomes more evident. As paraspinal muscles weaken, lordosis develops and abdomen is seen to be protuberant. Waddle develops due to the weakness of gluteal muscles, in particular, gluteus medius **(Box 2)**. At this stage, the quadriceps is often weakened, leading to episodes of knee buckling and falls which are spontaneous or result from small pushes and on uneven grounds.

BOX 2 Mechanism of waddling gait

Gluteus medius spans from iliac crest to the greater trochanter. In normal individuals, when one leg is raised off the ground, opposite gluteus medius contracts, keeping both anterior superior iliac spines at same level. With a weakened medius, pelvis tilts to the side of the raised leg, this alternates as child walks, resulting in waddle.

As the condition advances, extensors of the knee and hip joints become further weak and children find it more difficult to stand

Figures 3A to E Gower's sign

on their own and gradually take to the wheel chair. This stage is reached between 9–12 years, ambulatory being maintained longer in those who are on physiotherapy programs and use orthoses.

Contractures are seen in many muscles. In the initial stages, they are seen in the tendoachillis and the ilio-tibial bands. When the child becomes wheelchair hound, they become more pronounced and affect the knee and the hip areas. This makes it further difficult for the child to find a restful position for sleep and children sleep with knees bent, tilted to a side. The spinal deformities also increase, kyphoscoliosis adds to the problems of respiratory dysfunction.

On Examination

Hypertrophy Muscle hypertrophy is seen most prominent in the calves, but many other muscles like deltoids, brachioradialis, infraspinatus, glutii, temporalis and tongue are enlarged in size. The enlarged muscles are rubbery in consistency. As the disease advances, hypertrophy becomes less evident and the above-mentioned muscles reduce in size. Gastrocnemius and deltoid muscles often continue to remain large till late in the disease. In an occasional patient, no hypertrophy is seen.

Weakness Weakness of the muscles initially involves the lower limbs. It begins in the quadriceps and gluteal musculature and then tibialis anterior is weakened, resulting in foot drop. At this stage, children begin to walk on toes. Upper girdle weakness follows and is seen in serreti, lower part of pectorals, latissimus dorsi, biceps, and brachioradialis muscles. Weakness of the serratus anterior, lower trapezius and rhomboids causes winging of scapulae. The ocular, facial, bulbar and hand muscles are usually spared.

Because of simultaneous hypertrophy of deltoid superolaterally, infraspinatus inferomedially and wasting of posterior axillary fold, the appearance looks like valley (valley sign). It is best seen while arm abducted to 90° (or best possible abduction if 90° abduction is not possible) and hand facing upward, examiner observing the posterior shoulder girdle **(Fig. 4)**.

Reflexes Deep tendon reflexes are depressed in weak muscles and ankle reflex continues to be elicited till very late in the disease.

Cardiac findings Cardiac muscle is also involved in DMD leading the hypocontractility, dilated cardiomyopathy. Cardiac involvement starts early and subclinical disease is seen in one-fourth of patients under 6 years of age. Overt cardiac symptoms begin after 10 years of age, one-third of patients are symptomatic by 14 years and it is present in all patients over 18 years of age. Cardiac conduction defects are less commonly seen.

Figure 4 Valley sign

Respiratory involvement Restrictive lung disease is common. Vital capacity begins to diminish around 10 years of age, reducing at the rate of 10%/year approximately. As the vital capacity goes below 1 liter, the complication rates increase. Obstructive sleep apnea is seen in DMD children as early as the 1st decade and as vital capacity decreases further in the 2nd decade, children hypoventilate. Sleep disturbances due to both the respiratory changes are commonly encountered.

Intelligence The average intelligence of DMD tends to be lower and patients tend to have lower values of the verbal IQ. Attention deficit disorders may also be seen in minority of patients.

Orthopedic complications Scoliosis, long bone fractures due to falls, osteoporosis.

Malignant hyperthermia No clear association. But increased risk if exposed to halothane or succinylcholine.

Becker Muscular Dystrophy

This is a milder clinical form of dystrophinopathies. The onset is much later, mean age 12 years (range 5–45 years). Patients usually walk well into adult life. The weakness follows the pattern of DMD and cardiac involvement is less frequent.

Examination of the mothers of affected boys The majority are asymptomatic. However, a minority of carriers have clinically evident muscle weakness; the manifesting carriers. Some carriers experience muscle pains or cramps without weakness. Cardiac involvement is usually subclinical, but an occasional carrier may have severe cardiac failure. It is believed that carriers do not have reduced life expectancy.

Other phenotypes associated with dystrophinopathies (1) Exercise intolerance; (2) Myalgia; (3) Exertional myoglobinuria; (4) Isolated cardiomyopathy; and (5) Asymptomatic hyperCKemia. In general, familial cases with DMD seem to follow similar clinical courses but on occasions, striking intrafamilial phenotypic variability has been seen. Intrafamilial variation with same in-frame mutation is reported. Approximately 30% of patients have no family history of the disease and these represent spontaneous mutations.

Approach to Diagnosis

First, determine the phenotype of the index case; examine the family members and estimate serum muscle enzymes. Serum CK levels are markedly elevated in patients with DMD. The elevations are often extreme, being in thousands. The CK is elevated at birth and tends to rise by 3 years of age. They progressively decrease as the child gets weaker and the muscle mass is lost. Serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels are also increased commensurate with the CK elevation. This is important to recognize, as often children are unnecessarily investigated for hepatic dysfunction.

Molecular genetic testing Genetic studies are important for accurate diagnosis, genetic counseling and prenatal diagnosis. Multiplex polymerase chain reaction (PCR) has been used to study the *dystrophin* gene. PCR techniques study 19–32 exons covering the hot spots. These tests are able to detect the common deletions. Multiplex ligation dependent probe amplification (MLPA) is a more sensitive technique for detecting deletions. MLPA test studies all the 79 exon as and is able to detect duplications as well, increasing the yield by about 10%. If MLPA testing is negative, the DMD gene can be tested for point mutations. However, direct sequence analysis of the DMD gene is not widely available and exorbitantly expensive. Previously unidentified deep intronic mutations have recently been identified by a targeted high-density oligonucleotide microarray technique.

In India, multiplex PCR is regularly used in many centers in the research and service sectors while MLPA is available in fewer set-ups. Carrier detection requires the MLPA test, as it studies the dosing effect. Prenatal genetic diagnosis requires chorionic villus sampling and is available in India.

Electrodiagnosis Nerve conduction studies (NCV) are normal in early DMD. Only in advanced disease, the compound muscle action potentials (CMAP) may tend to decrease in amplitude. Needle EMGs confirm the myopathies nature of the illness by showing short duration, low-amplitude polyphasic motor unit potentials, particularly in proximal muscles **(Fig. 5)**. Some children have increased spontaneous activity which is believed to be due to reinnervation. As muscle mass reduces with advancement of the disease, motor units become progressively smaller and silent in some areas. Electrodiagnosis should be scheduled after collection of blood for CK level, as CK rises after needling of muscles. Also, it is preferable to avoid needle tests on muscles on which biopsy is planned.

Muscle biopsy Indication of biopsy in recent years is limited to situations where in clinical phenotype is atypical or genetic test is negative. Muscle with MRC grade 3–4 power should be selected for biopsy. The muscle tissue should be snap frozen in chilled isopentane to preserve the enzymes. Light microscopy shows degenerating necrotic muscle fibers with invasion of macrophages, as well as clusters of regenerating muscle fibers which have basophilic cytoplasm **(Fig. 6)**. Increased variability of muscle fiber size is common; fibers are initially larger than normal and become smaller later on. Histochemistry with ATPase shows type 1 fiber predominance. In advance stages, significant replacement of fibers by fat and endomysial connective tissue is seen. Immunostaining confirms absence of dystrophin **(Fig. 7)**. Three antibodies (Dys 1,

Figure 6 Muscle biopsy H & E stain: fiber size variation, myophagocytosis and regenerating fibers are seen

2 and 3) are available against dystrophin. They cover the carboxy terminus, central region and amino terminus. As each antibody covers only a portion of the protein, all three should be preferably used. In dystrophin deficiency as seen in BMD, the protein staining is irregular and fragmented.

Carrier females CK level are raised in half of known carriers. MLPA can detect the carrier status.

Management

General Management and Surveillance *(Table 2)*
In India, schools are not uniformly sensitized to the needs of DMD children and issues arising out of the special motor requirements of the child need to be individually addressed. Parental overprotection is common and many children do not attend school, resorting to tuitions at home. Behavior difficulties are common with DMD children and counseling of the whole family unit can be beneficial.

Corticosteroid Therapy
Proposed mechanisms Alteration of regulation of genes in muscle fibers, slowing of the rate of skeletal muscle breakdown, reducing

Figure 5 EMG showing myopathic discharges
Source: Dr Khushnuma Mansukhani, Department of Electrophysiology, Bombay Hospital Institute of Medical Sciences, Mumbai.
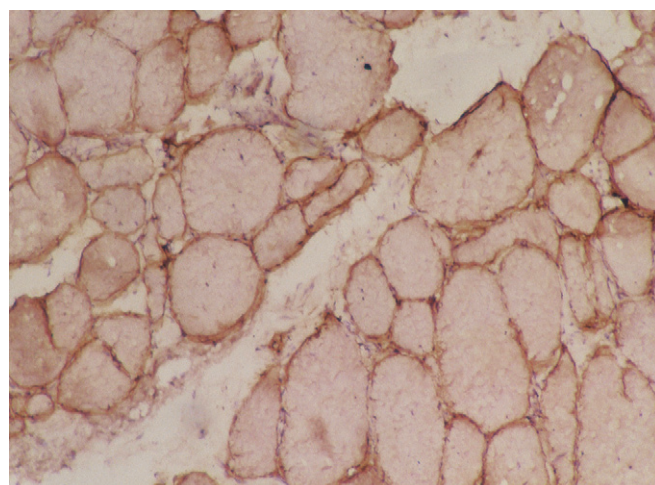
Figure 7 Normal immunostaining for Dystrophin 1. Note the brown staining of the sarcolemma (The muscle membrane does not take-up the stain in dystrophin deficiency)

Table 2 General management and surveillance in DMD

Cardiac	• Surveillance after 10 years of age • Annual ECG, 2D ECHO; Holter (if rhythm disturbance present) • ACEI, beta blocker
Respiratory	• Surveillance before ambulation lost—annually; afterward—frequently • Polysomnography • Early management of respiratory infection • Vaccination—influenza, pneumococci • NIPPV—Noninvasive positive pressure ventilation • Ventilatory support
Scoliosis	• Surveillance after 5 years of age • Surgery if degree of scoliosis is > 25% and vital capacity > 30% of predicted • Calcium and vitamin D supplement
Contracture	• Exercise program • Tendon release surgery

Figure 8 Exon skipping in DMD

cytotoxic T-cells, lowering cytosolic calcium concentrations and increasing myogenic repair.

Optimum dose Prednisolone/Prednisone: 0.75 mg/kg/day (Lower dose 0.3 mg/kg/day result in lesser degree of benefit and higher dose 1.5 mg/kg/day do not result in additional benefits).

Dosing regimens 1.25 mg/kg and 2.5 mg/kg alternate day doses; 10 days on and 10 days off; 10 days on and 20 days off; followed by 5 mg/kg/dose twice weekly. *Deflazacort*: 0.9 mg/kg/day is another option.

It is generally believed that corticosteroid treatment should be started early in the course of the disease but the optimal duration of the therapy is unclear. Trials show improved muscle strength within 10 days, which is maximal at 3 months and is maintained up to 18 months. Side effects of corticosteroids should be monitored and treated timely. Prednisolone and deflazacort have similar efficacy but different side effect profiles. FOR-DMD trial is expected to gives us clear idea about dose optimization and therapeutic window of prednisolone versus deflazacort. In India, where prevalence of tuberculosis is high, corticosteroid treatment may flair up underlying tuberculosis.

Drugs like oxandrolone, azathioprine, cyclosporine, creatine monohydrate, nifedipine, leucine, selenium and vitamin E, and antiserotonergic drugs methysergide and pizotifen have been tried in research settings, without robust evidence towards benefit.

Gene Therapy

Viral vectors The *DMD* gene is very large and, hence, it is difficult to have a viral vector to carry the entire gene. Critical fragments of the gene can be carried by adeno associated viral vectors. Such microdystrophin and minidystrophin genes have been injected in mice and dystrophin has been successfully expressed. How to provide the gene to multiple muscles groups is an issue as is the potential downsides of persistent immunomodulation amongst the recipients.

Antisense oligonucleotide exon skipping (Fig. 8) This technique can be used to redirect splicing which induces exon skipping and thus helps production of the functioning dystrophin. However, the antisense oligonucleotide has to be tailored to the deletion which is a limitation. Providing sustained therapy is another unanswered issue.

Read through stop codon strategies Gentamicin and PTC 124 have been studied. Gentamicin have not been successful in clinical
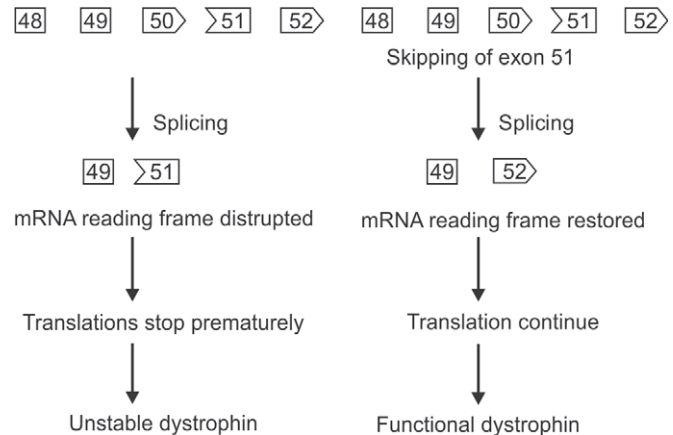
trials. PTC 124 is under trial. A possibility of global read through is a potential a risk of this therapy.

Stem cell therapy Myoblast transfer and bone marrow derived stem cell transfer has been used in research settings. Mesenchymal stem cell sources presently appear most promising.

Box 3 shows an approach to patient with DMD.

Outcome
Death is usually the result of pulmonary infections and respiratory failure and sometimes, of cardiac decompensation.

Prevention
The most relevant part of the genetic advances is the ability to prevent the further occurrence of the disease in families. Hence, all families having a DMD patient should be referred for genetic counseling. Detection and counseling of female carrier is an important step in the preventive management. Prenatal diagnosis should be pursued for carrier mothers, and is most helpful when deletion is detected in the index case. Chorionic villus sample is tested for the DMD gene at 10–12 weeks of gestation and affected conception is medically terminated. It is important to remember that germline mosaicism can go undetected when the carrier testing is performed. When mosaicism exists, the risk for future pregnancies is considered to be approximately 10–20%.

BOX 3 Approach to Duchenne muscular dystrophy

Clinical
• Male child
• Childhood onset progressive proximal muscle weakness [Gower's sign]
• Pseudohypertrophy of muscles especially calf
• Normal birth history
• Contributory family history

Investigation
• Serum creatine kinase
• EDX [particularly if inconclusive CK level]
• Molecular genetic testing
• Muscle biopsy with immunostain for dystrophin [if genetic testing is not available or informative]

Management
• General supportive care
• Corticosteroids
• Gene therapy

EMERY-DREIFUSS MUSCULAR DYSTROPHY

This muscular dystrophy is relatively benign X-linked recessive dystrophy characterized by contractures. Gene is located on *Xq28*, encode for the protein, Emerin, which is a protein on the nuclear membrane. Emerin plays a role in the attachment of nuclear membrane to heterochromatin.

Clinical Features

Age of onset varies from childhood to late adolescence or adulthood. Weakness initially affects the upper arm and pectoral girdle musculature and later the pelvic girdle and the distal muscles in the lower extremities. Early appearance of contractures in the flexors of the elbow, extensors of the neck, paraspinal muscles and achillis tendon is an important diagnostic clue.

On examination, during movement the contractures may feel almost bony, rather than a tight tendon. Occasionally facial muscles are affected. There is no hypertrophy or pseudohypertrophy. Mentation is unaffected. Cardiac conduction defects are common accompaniments. Female carriers are known to develop cardiac conduction defects, much later than patients.

Management

Diagnosis Strong clinical suspicion followed by DNA studies confirms the diagnosis. Emerin is expressed in skin as well and hence skin biopsy can be used for the diagnosis in place of muscle. CK levels may be elevated. Muscle biopsy and EMG favor myopathy.

Treatment There is no cure. Management is supportive. Cardiac abnormalities require monitoring. Atrial blocks can manifest suddenly and be fatal, hence pacemaker should be considered early in the disease. Female carriers need screening with ECG in 3rd decade and later.

Sporadic and autosomal dominant forms are also known with similar presentations, due to defect in lamin or nesprin. Half of the cases have none of known mutations, making understanding of this syndrome more complex.

CONGENITAL MUSCULAR DYSTROPHY

Congenital muscular dystrophies (CMD or MDC) have autosomal recessive inheritance. They announce themselves at birth with hypotonia and severe weakness **(Fig. 9)**. Intellectual disability may be present. Joint contractures are prominent, particularly at large joints of the lower limbs. MRI brain shows white matter signals **(Fig. 10)**. **Table 3** describes salient features of individual CMD. These are discussed in detail in next Chapter 43.7. Merosinopathy and Fukuyama muscular dystrophies are briefly described here.

MDC 1A: Merosinopathy

Laminin α2 (merosin) is a family of glycosylated proteins located in basement membrane. It is made of three chains: α2, β1, and γ1 and attaches to the dystroglycan complex. It is present in muscle, skin and peripheral nerves.

Figure 9 Merosinopathy. Note the anterior axillary fold suggesting pectorlis weakness
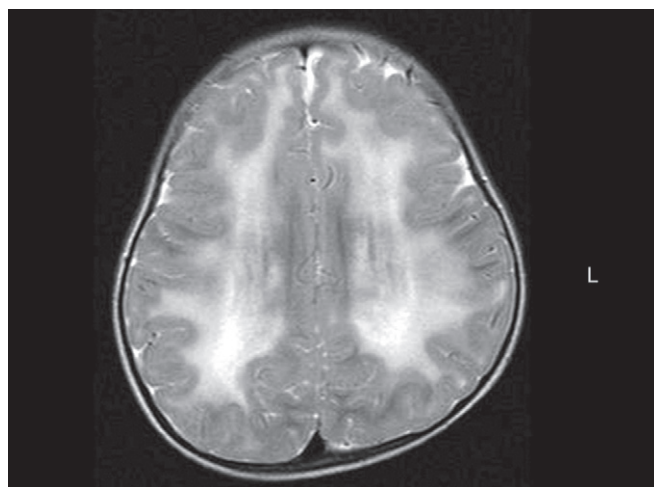
Figure 10 Merosinopathy MRI brain showing diffuse white matter changes
Source: Dr Sunila Jaggi, Department of Radiodiagnosis, Bombay Hospital Institute of Medical Sciences, Mumbai.

Table 3 Congenital muscular dystrophy

MDC	Inheritance	Gene locus	Protein	Creatine kinase	EMG
CMD/MDC 1A	AR	6q22–23	Laminin α2 chain (merosin)	Elevated	Myopathic with slowed nerve conduction velocities
CMD/MDC 1B	AR	12q13	α7 integrin		
CMD/MDC 1C/LGMD 2I	AR	19q13	FKRP		
Fukuyama/LGMD 2L	AR	9q31–33	Fukutin	Markedly elevated	Myogenic ± Neurogenic
WWS/LGMD 2K	AR	9q31	POMT1		
MEB disease/LGMD 2N	AR	1p32	POMGnT1		
Rigid spine syndrome	AR	1p35–36	Selenoprotein N1	Normal or slightly elevated	
Ullrich/Bethlem	AR/AD	21q22.3; 2q37	Collegens 6A1, 6A2, 6A3	Normal or slightly elevated	

Abbreviations: CMD/MDC, Congenital muscular dystrophy; LGMD, limb-girdle muscular dystrophy; WWS, Walker-Walberg syndrome; MEB, muscle eye brain disease.

Clinical features Patients present with severe weakness of the trunk and limbs and hypotonia at birth. Extraocular muscles are usually spared. Prominent contractures of the feet and hips are present. Intelligence is often normal. One-fifth of patients have epilepsy. Milder form with delayed onset of symptoms and mild weakness is known.

Management Skin or muscle biopsy reveals merosin deficiency. The final diagnosis depends on genetic confirmation because merosin reduction can also be a secondary phenomenon. Patients with merosinopathy often remain weak, have reduced quality of life and need external help and care.

Fukuyama Muscular Dystrophy

Fukutin is an enzyme associated with the golgi complex that takes part in glycosylation. Mutation leads to severe CNS manifestations associated with Fukuyama type muscular dystrophy because glycoprotein-dystrophin complex is expressed in the CNS and muscles.

Clinical features Children are usually normal at birth. Joint contractures affecting multiple large joints develop after few months. Such children are weak and may not be able to walk. They are also severely retarded and speech does not develop well in many children. Dependent existence is the norm.

Diagnosis Muscle biopsy shows changes of finer size variation, internal nucleation, increased fibrosis and presence of inflammatory cells. In a minority of patients, features of neurogenic changes may be seen in some areas. MRI scans confirm widespread white matter changes, more prominent in the anterior areas. Other brain malformations like malformations of the gyri have been shown on postmortem examinations.

Combination of muscular dystrophy, lissencephaly, cerebellar malformations, severe retinal and eye malformations are seen in Walker-Walberg syndrome (WWS) and muscle eye brain (MEB) disease. WWS is more severe form than MEB.

MYOTONIC DISORDERS

- Myotonic dystrophies: DM1, DM2, DM3
- Nondystrophic myotonias:
  - *Sodium channel*: Paramyotonia congenita, potassium sensitive, hyperkalemic periodic paralysis
  - *Chloride channel*: Becker (AR), Thomsen (AD).

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is characterized by muscle weakness, myotonia and systemic abnormalities like baldness, early cataracts, gynecomastia, etc. It is an autosomal dominant disease and the mutations are seen in myotonic dystrophy protein kinase (*DMPK*) gene, located on chromosome 19q13.3. It is a triplet repeat disorder (CTG). Normal individuals have between 5 and 30 repeats while patients have expansions going beyond 100. Disease severity correlates with the number of repeats. It is also important to realize that different body tissues have different repeat numbers and hence are affected with variable severities. Hence, it is not safe to prognosticate on the number of repeats in the peripheral blood. Anticipation is common in DM1 and maternal transmissions usually result in severe presentations.

Clinical Features

The illness usually begins in 2nd decade of life. The presenting weakness can be distal, leading to diagnostic difficulties. Patients have low set ears, open mouth, long face, temporal hollowing and wasting and weakness of sternocleidomastoid muscles **(Figs 11A and B)**. Shoulder and hip girdles are weak and gastrocnemius and hamstrings are often uninvolved. Ptosis and external ocular

Figures 11A and B Myotonic dystrophy: (A) Swan neck; (B) Hatchet face

movement paresis is seen in some individuals and palatal weakness leads to change in voice. As the muscles get weaker, myotonia becomes less prominent and may eventually be lost.

The child often becomes accustomed to the myotonia and does not complain about it and examiner has to ask leading questions like difficulty in relaxation of hand grip, to elicit the history. The demonstration of myotonia is done either by percussion of the muscle with a reflex hammer or after firm voluntary contraction. Examiner looks for difficulty in relaxation of the muscle after sustained contraction or a sharp tap. Percussion myotonia can be checked by percussion of the thenar eminence or of posterior muscles of forearm.

Systemic manifestations Mild to moderate mental retardation, cardiac conduction disturbances and tachyarrhythmias, excessive day time somnolence, enhanced sensitivity to barbiturates and morphine, premature cataracts having Christmas tree like appearance and endocrine abnormalities of thyroid, pancreas, hypothalamus and gonads are all seen in varying severities in patients of DM1.

Management

Definitive diagnosis is achieved by DNA analysis. EMG study elicits a characteristic sound called dive bomber or motorcycle potentials **(Fig. 12)**. Muscle enzymes are often abnormal. Drugs to treat myotonia include quinine, phenytoin, procainamide, mexiletine and acetazolamide. Supportive treatment consists of ankle foot orthoses for foot drop, wrist splints; modafinil for hypersomnolence and screening of family members.

Congenital Myotonic Dystrophy

This is seen in children of myotonic mothers. Cardinal features are hypotonia, facial paralysis, failure to thrive, feeding difficulties and mental retardation. Repeated respiratory infections are encountered. Poor fetal movements and polyhydramnios indicate that symptoms begin in intrauterine life. Severe weakness of face, jaw and elevated diaphragm with thin ribs on a chest X-ray provide a clue to the diagnosis. Congenital DM is almost always due to large unstable CTG repeat expansions occurring during maternal transmission. Examination of the mother with milder clinical features of DM confirms the diagnosis.

Limb-Girdle Muscular Dystrophies

Autosomal dominant limb-girdle muscular dystrophies (LGMDs) are termed type 1 while recessives form type 2. As a group, LGMDs present in 2nd or 3rd decades of life but some forms can be seen
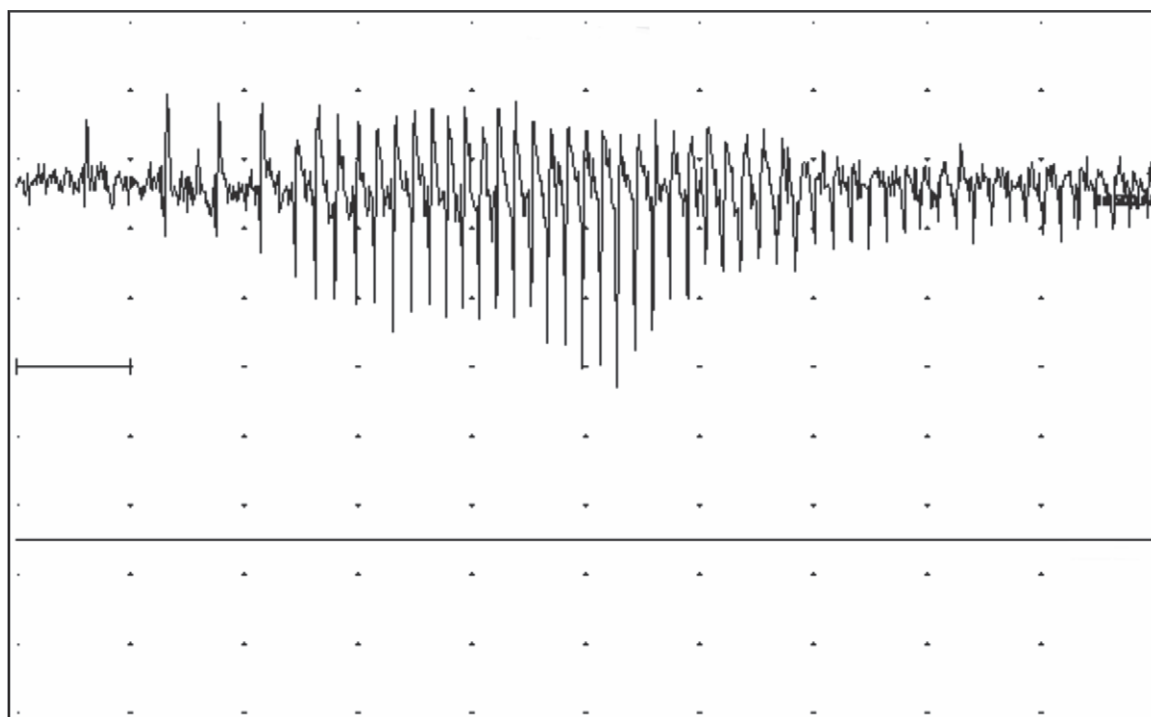
Figure 12 EMG showing myotonic discharges
Source: Dr Khushnuma Mansukhani, Department of Electrophysiology, Bombay Hospital Institute of Medical Sciences, Mumbai.

in younger children and hence are important to pediatricians. As consanguinity is a custom in some communities in India and hence autosomal recessive LGMDs are seen frequently.

Many forms of LGMD have been documented **(Table 4)** in literature. Amongst these, α- and γ-sarcoglycanopathies and α-dystroglycanopathies are more likely to present in 1st decade of life. When they do so, the clinical presentation is similar to DMD, with large calves, proximal weakness, Gower sign and toe walk. As these are autosomal, girls can be severely affected as well. When female members are not affected in sarcoglycanopathies, the differentiation from DMD becomes difficult. Patient with DMD are more likely to have significant heart involvement and mental sub-normality than LGMD. LGMD 2K, 2M, 2N and 2O are called the α-dystroglycanopathies. At times, children can present as congenital muscular dystrophy, very early in life.

In LGMDs, selective involvement muscle groups leads to unique appearance in muscles **(Box 4)**. Symptomatic cardiac involvement is more common in autosomal dominant LGMDs than autosomal recessive. Conduction defects and cardiomyopathies are known. The autosomal recessive types of LGMD are associated with a much higher level of CK elevation than the dominant forms of LGMD, with exception of LGMD1C. Further, within the recessive forms, LGMD2B, 2I and sarcoglycanopathies are usually associated with very high CK levels.

BOX 4 Selective involvement of muscle groups

- *Lumps and bumps* of quadriceps in LGMDs
- *Biceps lump* in dysferlinopathy **(Fig. 13)**
- *Diamond sign* (prominence of anterolateral aspects of thigh on partial contraction of quadriceps) in dysferlinopathy
- *Calf head on trophy sign* in miyoshi myopathy.

Presence of inflammatory cells in various types of LGMDs, especially in dysferlinopathy, often leads to an erroneous diagnosis of inflammatory myopathy. However, unlike polymyositis, the inflammatory cells usually do not invade non-necrotic muscle fibers. Hence, evaluation of all changes in the biopsy is important. In calpainopathies, the inflammatory cell infiltrate may contain eosinophils, leading to confusion with eosinophilia myositis. Muscle biopsy immunoanalysis can suggest the diagnosis in almost 70% LGMDs. Western blotting of these proteins is more reliable in deciding primary and secondary deficits. Mutation testing is now the gold standard for diagnosis. A firm diagnosis provides management guidance, including the need for cardiac and respiratory surveillance which is particularly important in LGMD 1B, 2C-F and 2I.

Facioscapulohumeral Dystrophy

This is a slowly progressive autosomal dominant muscular dystrophy. Two variant are known. The typical or facioscapulo-humeral dystrophy (FSHD) 1, results from deletion in a 3.3 kb repeating sequence termed as D4Z4 at chromosome 4q35. Approximately 5% patients with FSHD have hypomethylation of this sequence, termed FSHD 2. The responsible gene is DUX4. Over expression of DUX4 is a result of hypomethylation and dysregulation of transcription of other genes. In FSHD1 larger size of the deletion leads to a more severe disease.

Clinical features Facioscapulohumeral dystrophy usually presents in adolescence. Patients have shoulder girdle and bifacial weakness **(Figs 13 and 14)**. The fixators of scapula are particularly weakened and lead to chicken wing appearance. Over-riding of scapula restricts abduction of shoulder and gives false impression of deltoid weakness. The deltoid muscles are in fact strong till late in the illness. Usually biceps waste less than the triceps, and the brachioradialis muscles even less, gives Popeye effect (thin upper arm and relatively preserved forearm). Wrist flexors are usually stronger than the extensors. Unlike most muscular dystrophies, FSHD tends to be asymmetrical, at times remarkably so. In the lower limbs, hip flexors, quadriceps, ankle dorsiflexion followed by ankle plantar flexion is the usual order of involvement. Weakness of ankle dorsiflexion in face of stronger plantar flexion leads to

Table 4 Limb-girdle muscular dystrophy (LGMD)

LGMD	Gene locus	Protein	Protein function	Age of onset	Key features
1A	5q22.3–31.3	Myotilin	Myofibrillogenesis and stabilization of the Z-disk and sarcomere	Adulthood	Dysarthria, dysphagia, tight TAs, distal weakness, cataract, cardiac and respiratory complications
1B	1q11–21 (allelic to AD-EDMD)	Lamin A and C	Nuclear envelop protein interact with various lamin associated proteins including emerin	Any age	Family history of sudden death, joint contractures, rigid spine, cardiac and respiratory complications
1C	3p25	Caveolin 3	Scaffolding proteins that interact with lipids and other proteins in caveoli (flasked shaped invaginations of the sarcolemmal membrane)	Any age	Muscle rippling, myalgia, normal sporting ability in childhood, cardiac (rare)
1D	6q23	?			
1E	7q	?			
2A	15q15.1–21.1	Calpain 3	Enzyme, regulatory role in the modulation and control of transcription factors and thus of gene expression	1st–2nd decade	Toe-walking, scapular winging (whole of the medial scapular border jutting backward), early contracture, retained respiratory function; Early involvement of the posterior thigh muscles (adductors, semimembranosus and Vastus intermedius) with relative sparing of the Vastus lateralis, Sartorius and gracilis. Early involvement of rectus abdominis muscle.
2B	2p13	Dysferlin	Important in membrane repair	2nd–3rd decade	Inability to walk on tiptoe, sudden onset calf pain and swelling—may be misdiagnosed as myositis
2C 2D 2E 2F	13q12 17q12–21.3 4q12 5q33–34	γ-sarcoglycan α-sarcoglycan β-sarcoglycan δ-sarcoglycan	When one is absent, the others may be missing. Part of α-dystroglycan in plasma membrane	1st–2nd decade	Muscular hypertrophy- calf and tongue, cardiomyopathy, scapular winging. α-relatively milder type
2G	17q11–12	Telethonin	Normal myofibrillogenesis	2nd decade	Distal weakness and wasting (foot drop), calf hypertrophy ±, Rimmed vacuoles
2H	9q31–33	E3 ubiquitin ligase (TRIM 32)	Regulation of myofibrillar protein turnover	2nd decade	Mild facial weakness
2I	19q13	FKRP	Glycosyltransferase: Glycosylation of α-dystroglycan	1st–2nd decade	
2J	2q31	Titin		1st–4th decade	
2K	9q31	POMT 1		Birth–6 years	May present early with global delay, upper limb weakness may be worse than lower limb weakness, hypertrophy ±, cognitive impairment, microcephaly
2L	11p14.3	Anoctamin 5	Calcium activated chloride channel	11–50 years	Quadriceps atrophy, myalgias
2M	9q31–33	Fukutin		< 1 year	
2N	1p32	POMGnT1		< 2 years	
2O	14q24	POMT 2			

Figure 13 Biceps lump in dysferlinopathy

Figure 14 FSHD: winging and riding of the scapulae

Table 5 Distal muscular dystrophy

Distal dystrophies	Inheritance	Gene locus	Protein	Age of presentation (years)	Predominant muscle group involves	CK	Rimmed vacuoles	Important point
Miyoshi 1	AR	2p13	Dysferlin	Adolescence	Posterior compartment of leg	10–50 ×	–	
Nonaka	AR	9p1–q1	GNE	Before 30	Anterior leg compartment and wrist and finger extensors, Quadriceps sparing	3–10 ×	+	Hereditary inclusion body myopathy, Reduction in sialic acid production
Laing	AD	14q11	Myosin heavy chain 7 (MyHC 7)	Childhood or early adulthood	Anterior leg compartment and neck flexors	3 ×	–	Cardiomyopathy

Abbreviations: AR, autosomal recessive; AD, autosomal dominant; CK, creatine kinase; EMG, electromyography; FKRP, Fukutin-related protein; POMT, Protein O-mannosyltransferase 1; POMGnT, O-mannose-β-1,2-N-acetylglucosaminyltransferase; GNE, glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; ACEI, angiotensin converting enzyme inhibitors.

equinovarus contracture of foot, making the use of an ankle foot orthoses impossible. The Beevor sign, an upward movement of the umbilicus on flexing the neck as a result of weakness of the lower abdominal muscles, is common. Severe infantile form is well known. Association with sensorineural hearing loss and exudative retinal detachment (Coats' disease) exists in minority of patients. Frequently examination of family members for subtle signs of facial weakness or scapular winging gives immediate diagnostic clue. Other known phenotypic variants are (a) the face sparing variant, (b) with external ophthalmoplegia and (c) limb-girdle pattern of weakness.

Management Serum CK level is elevated several folds above normal. EMG shows myopathic potentials. Muscle biopsy shows dystrophic changes with characteristic angular fibers. Dystrophic changes may be less prominent in some biopsies, and the main change may be the angulated fibers, raising doubts about a neurogenic pathogenesis. DNA studies reliably establish the diagnosis. In indicated cases, surgical stabilization of scapula is beneficial. Trials of prednisolone or β-agonist (albuterol) have been known to result in transient benefits in a proportion of sufferers.

Distal Muscular Dystrophies

As distal weakness is more often a feature of neurogenic disorders, these myopathies are often confused with hereditary or acquired neuropathies or motor neuron disease. Sparing of the extensor digitorum brevis muscle is an important distinctive feature. Elevated CK and EMG distinguish it from neuropathic disorder. Other myopathies with distal weakness like myotonic dystrophy type 1, inclusion body myositis and myofibrillar myopathy form the differential diagnosis. Age of onset, inheritance pattern, histopathology, and pattern of weakness are most useful in distinguishing the individual distal myopathies. Although the group of distal myopathies starts distally or in some cases semi-distally, as the disease progresses, it involves proximal muscles. Distal myopathies patient are helped by symptomatic treatments like cock-up splint or ankle-foot orthoses.

Table 5 highlights salient features of individual distal myopathies. Markesbery-Griggs, Udd, and Welander are other distal myopathies presented in adulthood.

MORE ON THIS TOPIC

Angelini C, Peterle E. Old and new therapeutic developments in steroid treatment in Duchenne muscular dystrophy. Acta Myol. 2012;31:9-15.

Dastur R, Gaitonde P, Khadilkar S, et al. Becker muscular dystrophy in Indian patients: analysis of *dystrophin* gene deletion patterns. Neurol India. 2008;56:374-8.

Guglieri M, Bushby K. How to go about diagnosing and managing the limb-girdle muscular dystrophies. Neurol India. 2008;56:271-80.

Hoffman EP, Reeves E, Damsker J, et al. Novel approaches to corticosteroid treatment in Duchenne muscular dystrophy. Phys Med Rehabil Clin N Am. 2012;23:821-8.

Khadilkar S, Singh R. Limb girdle muscular dystrophies in India. Neurol India. 2008;56:281-8.

Khadilkar S. Bird's eye view of myopathies in India. Neurol India. 2008;56:225-8.

Mankodi A. Myotonic disorders. Neurol India. 2008;56:298-304.

Manshukhani K, Doshi B. Interpretation of electroneuromyographic studies in diseases of neuromuscular junction and myopathies. Neurol India. 2008;56:339-47.

Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2008;(1):CD003725.

Nadkarni J, Dastur R, Vishwanathan V, et al. Duchenne and Becker muscular dystrophies: an Indian update on genetics and rehabilitation. Neurol India. 2008;56:248-53.

Pradhan S. Valley sign in Duchenne muscular dystrophy: importance in patients with inconspicuous calves. Neurol India. 2002;50:184-6.

Wilton S, Fletcher S. Exon skipping and Duchenne muscular dystrophy: hope, hype and how feasible? Neurol India. 2008;56:254-62.

Yiu M, Kornberg A. Duchenne muscular dystrophy. Neurol India. 2008;56:236-47.

IN A NUTSHELL

1. DMD is X-linked recessive, the most common muscular dystrophy of young age with positive Gower sign, pseudohypertrophy of muscles, significantly elevated CK and readily diagnosed with the help of genetic testing.
2. BMD is a milder form of DMD, having better prognosis.
3. Upper limb onset, early contracture and cardiac complication favors the diagnosis of EMD.
4. Delay development since birth, intellectual disability, contracture and imaging abnormality suggests congenital muscular dystrophy.
5. Myotonia, systemic manifestation, weakness, positive family history and characteristic electrophysiological abnormalities confirm the diagnosis of myotonic dystrophy.
6. Asymmetrical differential muscle weakness in facial and upper girdle region with scapular winging suggests FSHD.
7. Limb-girdle muscular dystrophies consist of a wide group of autosomal muscular dystrophies having predominant proximal muscle weakness, contributory family history, variable elevated CK and variable systemic involvement. Weaker hip adductor over hip abduction favors LGMD more than DMD.

Chapter 43.7
Congenital Muscular Dystrophy
Sunil Pradhan, AK Meena

Congenital muscular dystrophy (CMD) is genetically heterogeneous group of disorders in which the affected infants typically appear *floppy* with low muscle tone, poor spontaneous movements, joint contractures and spinal rigidity. Muscle weakness which is predominantly proximal, typically presents at birth or early infancy and is very slowly progressive with periods of nearly stationary course in between. Joint contractures and spinal deformities contribute to the disability and respiratory compromise. Since delay of motor skill acquisition may be a presenting symptom of CMD, onset of manifestations before the age of two years is generally taken as important criteria for its diagnosis. The muscle weakness of CMD may be stable in the short-term, but typically over time the weakness and its related complications worsen. Apart from muscle, connective tissue and brain, heart and eye are the other organs which are often involved in this disorder.

The condition was first described by Batten in 1903 and subsequently the term congenital muscular dystrophy was coined by Howard in 1908. Other varieties of CMD were described by Ullrich in 1930 and Fukuyama in 1960. Later on, a Finnish variant called muscle-eye-brain disease or Walker-Warburg syndrome was described.

PREVALENCE

Fukuyama congenital muscular dystrophy is fairly common in Japan. It is approximately half as common as Duchenne muscular dystrophy (DMD). The estimated prevalence is approximately 7–12 cases per 100,000 children. The prevalence of all congenital muscular dystrophies has been estimated to be 4.7 cases per 100,000 children in Italy, while in Sweden the incidence is estimated at 6.3 cases per 100,000 births. Genetic mutations are identifiable in only about 25–50% of patients with CMD.

SUBTYPES

The CMD subtypes are mainly grouped on the basis of gene mutations and the abnormalities in the gene product **(Table 1)**. The common subtypes are: (1) laminin-α2 (merosin) deficiency (MDC1A), (2) collagen VI-deficient CMD, (3) *SEPN1*-related CMD (previously known as rigid spine syndrome, RSMD1), (4) dystroglycanopathies (caused by mutations in *POMT1, POMT2, FKTN, FKRP, LARGE, POMGNT1,* and *ISPD*) **(Box 1)**, and (5) *LMNA*-related CMD (L-CMD). Several less known CMD subtypes have been reported in a limited number of individuals.

Cognitive impairment ranging from intellectual disability to mild cognitive delay, structural brain and/or eye abnormalities, and seizures are found almost exclusively in the dystroglycanopathies while white matter abnormalities without major cognitive involvement tend to be seen in the laminin-α2-deficient subtype. Besides clinical similarities these genetically different disorders also have histopathological similarities. Muscle biopsy would

Table 1 Classification of congenital muscular dystrophy

	Subtype name	Gene symbol	Protein	Other subtype name or other phenotype
Defects of Structural Protein	Laminin alpha-2 deficiency (MDC1A)	*LAMA2*	Laminin α2	Merosin-deficient CMD
	Collagen VI-deficient CMD	*COL6A1* *COL6A2* *COL6A3*	Collagen VI Collagen VI Collagen VI	Ulrich CMD (UCMD)/Bethlem myopathy
	Integrin α7-deficient CMD		Integrin α7	
	CMD with epidermolysis bullosa		Plectin	
Defects of Glycosylation	Dystroglycanopathy	*POMT1*	Protein-O-mannosyltransferase 1	WWS LGMD2K
		POMT2	Protein-O-mannosyltransferase 2	WWS, LGMD2N
		FKTN	Fukutin	WWS, MEB-like CMD FCMD LGMD2M
		FKRP	Fukutin-related protein	WWS, MEB-like CMD, MDC1C LGMD2I
		LARGE	Large	WWS, MDC1D
		POMGNT1	O-linked mannose β1,2-N-acetylglucosaminyl-transferase	MEB, LGMD
		ISPD	Isoprenoid synthase domain-containing protein	WWS, LGMD
Defects of Proteins of the Endoplasmic Reticulum	*SEPN1-related myopathy*	*SEPN1*	Selenoprotein N	Rigid spine syndrome (RSMD1)
Defects of Nuclear Envelope Proteins	*LMNA-related CMD (L-CMD)*	*LMNA*	Lamin A/C	Dropped-head syndrome, EDMD
Mitochondrial membrane protein	CMD with mitochondrial structural abnormalities		Choline kinase beta	

Abbreviations: MDC1A, merosin-deficient congenital muscular dystrophy type 1A; MDC1C, merosin-deficient congenital muscular dystrophy type 1C (with muscle hypertrophy); MDC1D, merosin-deficient congenital muscular dystrophy type 1D (with intellectual disability and abnormal glycosylation); WWS, Walker-Warburg syndrome; FCMD, Fukuyama CMD; MEB, muscle-eye-brain (disease); CMD, congenital muscular dystrophy; LGMD2I, limb-girdle muscular dystrophy type 2I (no intellectual disability); LGMD2K, limb-girdle muscular dystrophy type 2K with microcephaly, intellectual disability, normal MRI; LGMD2M, limb-girdle muscular dystrophy type 2M (no intellectual disability); LGMD2N, congenital muscular dystrophy/limb-girdle muscular dystrophy type 2N (intellectual disability); EDMD, Emery-Dreifuss muscular dystrophy.

show dystrophic features such as small, round fibers with fiber-size variability, immature muscle fibers, and occasional necrotic muscle fibers along with a more characteristic finding of marked increase in endomysial and perimysial connective tissue. The inheritance of CMD is essentially autosomal recessive (AR) except some of the cases of collagen VI-deficient CMD and all the cases of LMNA-related CMD (L-CMD) which are inherited in an autosomal dominant manner (AD).

CLINICAL PRESENTATION OF SUBTYPES

CMD with Laminin-α2 Deficiency (MDC1A, Classic CMD, Merosin-Deficient CMD)

The most common CMD is laminin-α2 deficiency accounting for approximately 40% of all cases. It is characterized by decreased fetal movements. Infants may have gross hypotonia, feeding and breathing difficulties and weakness during the first few months of life. Contractures are common. Most children eventually attain sitting but standing and walking with support is acquired only in 25%. External ophthalmoplegia is rare and occurs late. Some may develop enlarged head. Weakness is static or minimally progressive, but children often die 10–30 years later due to respiratory failure. Cardiac abnormalities (in one-third of patients), respiratory failure, feeding difficulties and scoliosis are the associated complications. Some patients may have a sensory motor demyelinating neuropathy which may be insignificant. Seizures occur in 20–30% cases. Cognitive abilities are usually normal in spite of MRI findings that are visible after age 6 in the form of periventricular white-matter hypomyelination **(Figs 1A to D)**. Structural brain changes like enlargement of the lateral ventricles, focal cortical dysplasia, occipital polymicrogyria and/or agyria, and hypoplasia of the pons and/or cerebellum may be seen in some patients **(Figs 1A to D)**.

Apart from this classical presentation of laminin-α2 deficient CMD, three different clinical variants are known to exist. These are:
1. Some rare patients with partial laminin-α2 deficiency present with hypotonia during the first year, but they become ambulatory and maintain ambulation for many years.
2. Some may present with a limb-girdle phenotype or with a phenotype resembling rigid spine muscular dystrophy (RSMD) or Emery-Dreifuss muscular dystrophy. In such patients, MRI abnormalities, seizures, and demyelinating neuropathy are the clues to suspect laminin-α2 deficiency.
3. Patients with complete lack of merosin are more severely affected, often presenting within the first week of life, requiring ventilatory support and enteral feeding.

Collagen VI Deficient CMD

This subtype of CMD is due to mutation in the gene for collagen type VI. Although originally described as separate entities, Ullrich CMD and Bethlem myopathy represent a clinical continuum of Collagen VI deficient CMD; intermediate phenotypes are also common. Three phenotypes have been described in individuals with collagen VI myopathy: (1) early and severe (ambulation never achieved), (2) moderate progressive (ambulation attained and lost), (3) mild (ambulation into adulthood).

Ullrich Congenital Muscular Dystrophy

It is an autosomal recessive disorder due to mutation in the gene for collagen type VI. The characteristic features include hypotonia in the neonatal period, kyphosis of the spine, torticollis, facial dysmorphism (micrognathia, prominent ears drooping of lower eyelid and round facies) and hip dislocation. Proximal joint contractures and distal hyperlaxity are characteristic **(Figs 2A[a to h] and B[a to d])**. A protruding calcaneus may also be seen. Most patients never walk and the weakness involves more proximal than distal muscles. In children who walk, progressive disability, usually due to contractures, lead to loss of ambulation after 3–10 years. Lax joints may become contracted. Respiratory failure invariably develops in the first or second decade. Skin manifestations like follicular hyperkeratosis, keratosis pilaris, and keloids may be seen. Patients have normal intelligence and brain MRI.

Bethlem Myopathy

Bethlem myopathy is due to autosomal dominant mutations in the same gene for collagen type VI. It is the milder form of Ullrich CMD. Typical features of Bethlem myopathy include: Onset in the first or second decade, but it may be as late as sixth decade; Flexion contractures are seen in the fingers, wrists, elbows, and ankles. Contractures may improve in childhood. Patients have weakness involving proximal and respiratory muscles. Rarely patients have no weakness. Weakness is slowly progressive. Patients usually have a normal life expectancy. Mild improvement may occur around puberty. In adults, progression may result in need for a wheelchair after 40–50 years. In intermediate cases, features of both diseases are noted with childhood-onset weakness, Ullrich like distal laxity, and Bethlem like contractures of finger flexors. Severe cases are similar to Ullrich congenital muscular dystrophy. A limb girdle muscular dystrophy (LGMD*)* phenotype with no significant contractures has been described. Some cases present with contractures without weakness and a Woody feeling upon palpation of muscles (myosclerosis).

Congenital Muscular Dystrophy with Rigid Spine (RSMD1 or *SEPN1*-related CMD)

Clinical presentation is at birth or within the first year of life, with variable degrees of cervicoaxial weakness and hypotonia early in life. The clinical features are rather homogenous. Most patients eventually walk, but in rare and severe cases, patients never gain independent ambulation. Scapular winging and facial and bulbar weakness are common. In contrast to Ullrich congenital muscular dystrophy, contractures are not present at birth, but they usually develop at age 3–10 years. The most characteristic pattern is spinal rigidity and scoliosis. Contractures of the face, proximal limbs, and finger extensors may also be present. Body mass index may be low in some patients. Respiratory insufficiency is common and progressive and may be more severe than limb weakness. Ventilatory assistance may be needed as early as the first decade of life to treat nocturnal hypoventilation a distinct feature of this type of CMD. Ambulation may be maintained for many years. Heart is usually normal but conduction blocks have been reported. Mental retardation is not a feature and imaging of brain is normal. The condition results from mutation in the *SEPN1* gene
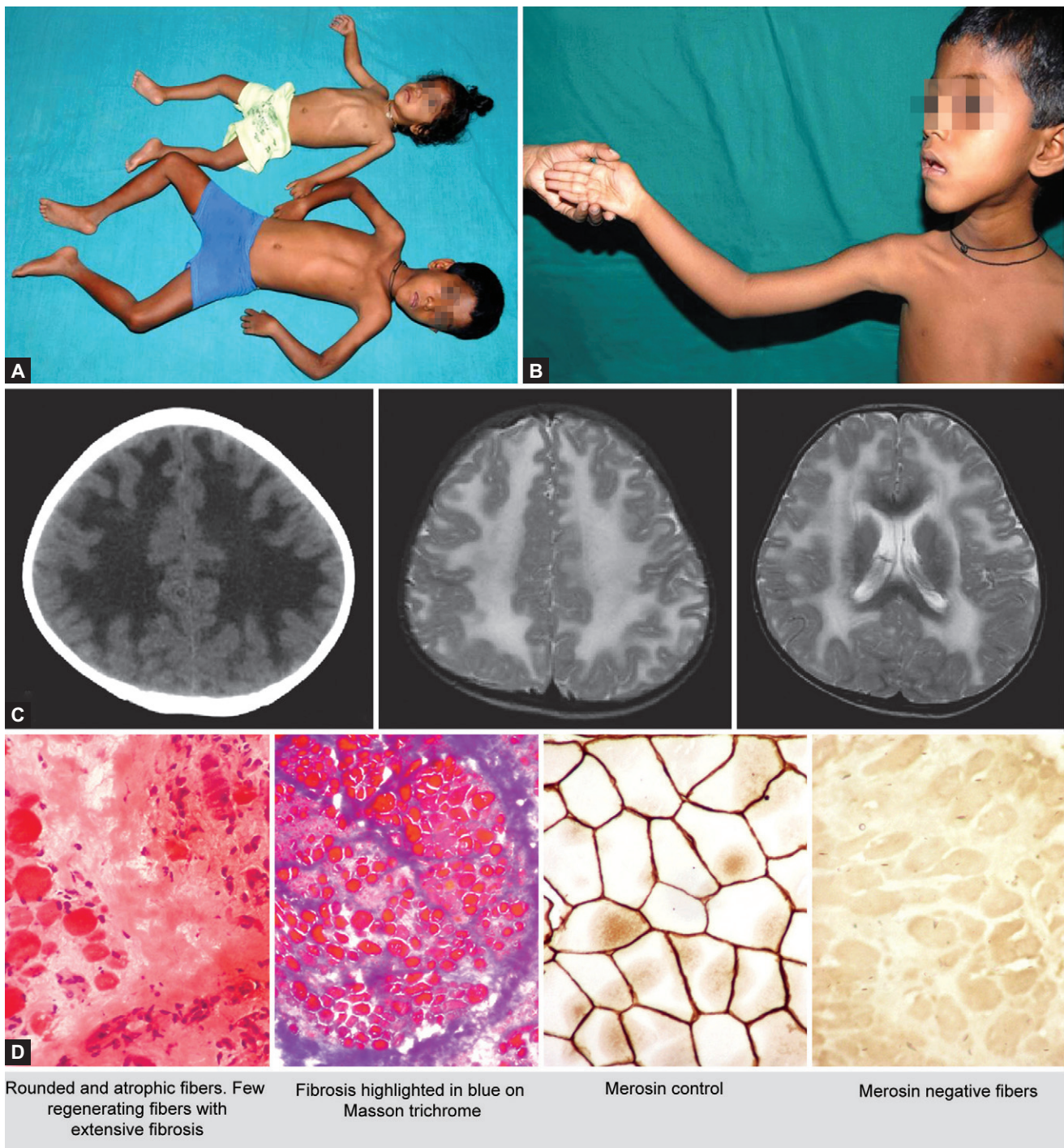
Figures 1A to D CMD with laminin-α2 deficiency. (A and B) Showing contractures in the patient; (C) MRI of brain showing hypointensity on T1 images and hyperintensity of white matter in T2 images suggesting hypomyelination; (D) Histology of merosin deficient congenital muscular dystrophy

that encodes for a protein found in endoplasmic reticulum called selenoprotein N.

There is another gene defect that results in a phenotype similar to axial muscular dystrophy similar to SEPN-1 related myopathies; in patients with a mutation in selenocysteine insertion sequence-binding protein 2 (SECISBP2, SBP2), there is a multisystem disorder that includes axial muscular dystrophy and other features such as azospermia, cutaneous photosensitivity, impaired T-cell proliferation, increased fat mass with enhanced insulin sensitivity, and hearing loss. MRI shows selective involvement of the sartorius

and major adductor muscles in the thigh. This gives a characteristic medial thigh wasting, notable on physical examination.

RSMD1 is caused by *SEPN1* mutations and has normal expression of the protein merosin. However it is now known that *rigid spine syndrome* is not specific to this subtype and that some spinal rigidity resulting from paraspinal contractures may develop in other CMD subtypes. *SEPN1* mutations are also reported in the classic form of multiminicore myopathy, in congenital fiber-type disproportion myopathy, and in a desminopathy with Mallory body-like inclusions.

Figures 2A (a to h) Ullrich congenital muscular dystrophy (UCMD). (a) Severe contracture of the shoulder, elbow joints, hips and knee joints, slender habitus with generalized muscle wasting and particularly of distal upper limb. (b) Hyperextensibility of the interphalangeal joints. (c) Hyperlaxity of the ankle joint. (d) Hyperextensibility of the wrist. (e) Classical protuberant calcanei. (f to h) Typical velvety palms and soles and almost total absence of the major palmar and plantar creases

Alpha-dystroglycanopathy (Glycosyltransferase Deficiency)

Initially, mutations in different genes were thought to cause separate disorders. Presently mutations in 12 genes involved in glycosylation of α-dystroglycan are known to cause congenital muscular dystrophy. It is now known that mutations in these genes result in overlapping phenotypes with a wide range of phenotypic heterogeneity. Similarly, a single phenotype can be caused by more than one gene mutation. In these CMDs, the severity of changes in affected tissue has an order of rank based on the degree of preserved α-dystroglycan function. In the mildest disease, only the skeletal muscle is affected. This is classified by online mendelian inheritance in man (OMIM) as type C; limb-girdle phenotype. Type B represents moderate dystrophic changes in the muscle resulting in congenital onset with or without mental retardation. As severity progresses, the cerebellum and then the pons, eyes, and cerebrum are affected. This most severe form is classified by OMIM as type A; congenital with brain and eye abnormalities. Again the eye and pontocerebral involvement may have mild to severe degree.

Each affected tissue shows an order of worsening severity. In mild disease, patients may have normal muscle and only mild eye and cerebellar abnormalities. In intermediate disease, patients may have mild dystrophic changes, myopia, pontocerebellar hypoplasia, and focal pachygyria. In severe disease, patients may have active muscle fiber degeneration and necrosis, nonfunctioning eyes, severe pontocerebellar hypoplasia, and agyria. In general brain, MRI may show structural abnormalities like hydrocephalus, brain stem hypoplasia, cerebellar cysts; or abnormalities in neuronal migration (cobblestone lissencephaly or polymicrogyria) **(Figs 3A to F)**. With time white matter changes may regress. Various forms [most severe forms are Fukuyama congenital muscular dystrophy (FCMD), Muscle-eye-brain (MEB) disease, Walker-Warburg syndrome (WWS)] of alpha-dystroglycanopathies are described below:

Fukuyama Congenital Muscular Dystrophy (Mutation in Fukutin)

Patients often present in utero with decreased fetal movements poor sucking, lack of head control, and a weak mouth in neonatal period. At age 2–8 years, most patients stand or walk few steps, but patients with severe disease may be able to sit only with
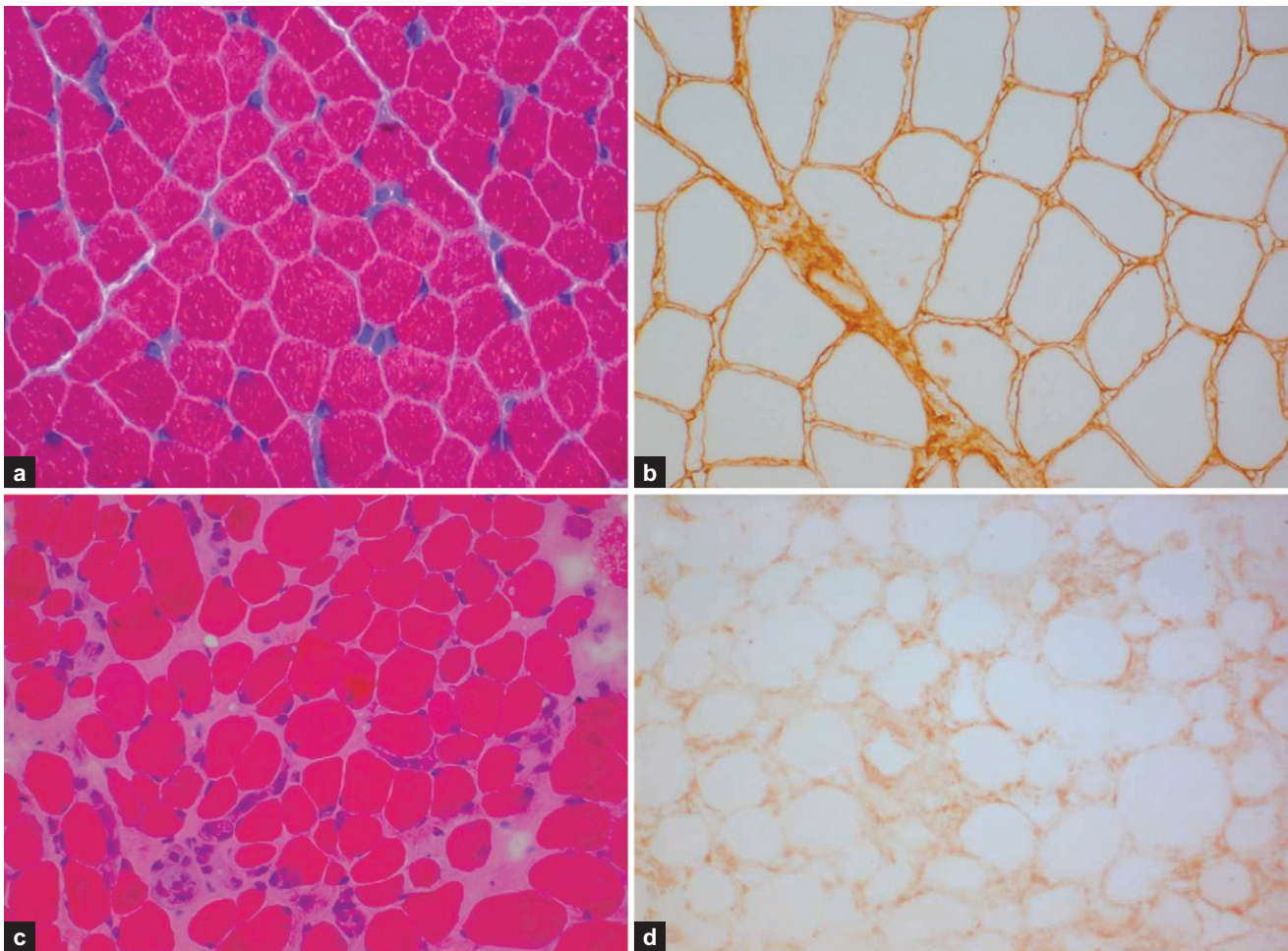
Figure 2B (a to d) Histology of UCMD: Transversely cut skeletal muscle tissue showing (a) normal polygonal fibers (HE) (b) Normal preserved expression of *Col6A1* in all fibers (c) rounding and variation in fiber diameter (HE) (d) loss of expression of *Col6A1* in all the fibers

support. Progressive weakness and respiratory failure follows, with death usually occurring in the mid teens. However, death can occur as late as the mid 20s or as early as age 2 years. Cardiac disease develops after the age of 10 years, resulting in dilated cardiomyopathy and congestive heart failure in most patients. Eye movement abnormalities, poor pursuits, and strabismus are seen in milder cases and retinal detachment, microphthalmos, cataracts, hyperopia, or severe myopia are seen in severe forms. Cerebral changes are always present which include Type II lissencephaly or cobblestone lissencephaly (a finding which is considered a classic finding in this disease as well as in all other glycosyl-transferase deficiencies), cobblestone polymicrogyria **(Figs 4A to C)** and/or pachygyria to complete agyria due to neuronal migration abnormalities, dysplasia of the pyramidal tracts, ventricular dilation and delayed myelination. Cerebellar cysts are common **(Fig. 4)**. Seizures occur in about 50% of patients. Mental retardation is usually present. Two families with three affected children with a limb girdle phenotype (LGMD2M) and a mutation in *fukutin was* reported. Onset was before 1 year with hypotonia. Deterioration occurred with febrile illness and there was improvement with corticosteroids. Intelligence and brain MRI were normal. Dilated cardiomyopathy with no or minimal limb girdle muscle involvement and normal intelligence can be the sole manifestation in 2nd to 5th decades.

Muscle-Eye-Brain (MEB) Disease

Mutations in *POMT1*, *POMT2*, *POMGnT1*, *FKRP,* and *LARGE* can cause this syndrome. The incidence varies in different studies. Severity of the phenotypes also varies. Severely affected patients cannot sit or turn, they lack visual contact, and they often die in the first 1–2 years. Moderately affected patients can often sit and speak a few words. They may have severe myopia, but they can make visual contact. Mildly affected patients may be able to walk for a short time, they can speak in sentences, and they have preserved vision. Seizures are common and severe but similar to those of Fukuyama congenital muscular dystrophy. CNS abnormalities are always present, including moderate-to-severe mental retardation. Cerebral changes are similar but variable to those of Fukuyama congenital muscular dystrophy.

Walker-Warburg Syndrome

It is the most severe form of congenital muscular dystrophy and is caused by mutations in all glycotransferases. They manifest in utero or at birth, with hypotonia, poor sucking, swallowing and contractures. It is progressive and the average time to death is 9 months. Associated eye abnormalities include microphthalmos, hypoplastic optic nerve, ocular colobomas, retinal detachment, cataracts, glaucoma, iris malformation, and corneal opacities, all leading to blindness. Complete type II lissencephaly with agyria, thin cortical mantle, an absent corpus callosum, fusion of the
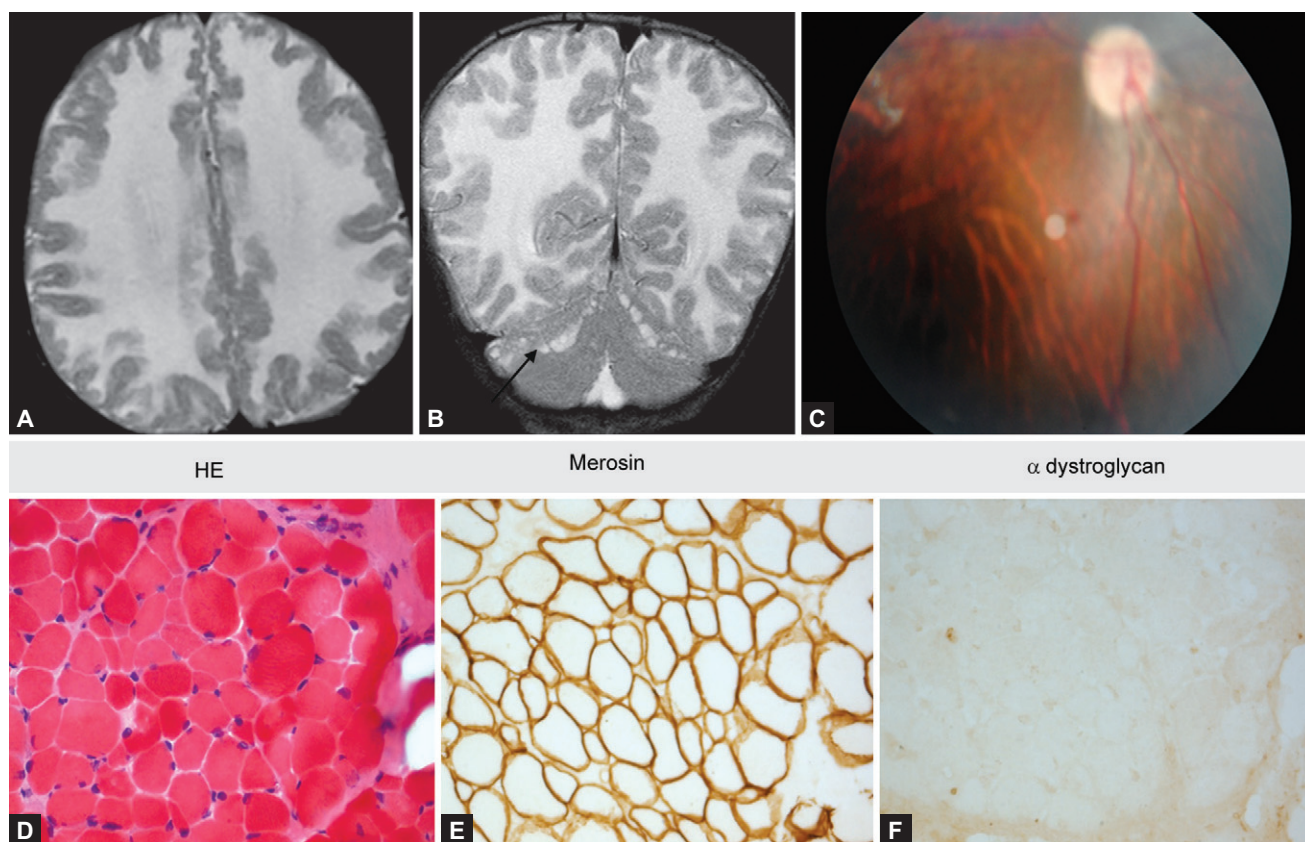
Figures 3A to F Alpha-dystroglycanopathy. (A and B) A 4-month-old male child with macrocephaly, development delay, seizures, hypotonia, brisk reflexes, ankle contractures, hypogonadism, EOM abnormality and high CK levels. MRI brain showing Type 2 (cobblestone) lissencephaly in the child diagnosed as Alpha dystroglycanopathy. [T1-weighted axial view and coronal view] The cortex shows a bumpy surface and is less markedly thickened than in type I lissencephaly. The underlying white matter is abnormally hyperintense due to abnormal myelination. In the posterior fossa cerebellar cortical dysgenesis is revealed by the bumpy surface of both hemispheres and multiple subcortical cysts (arrow). (C) Chorioretinitis with disc pallor. (D-F) Histology pictures
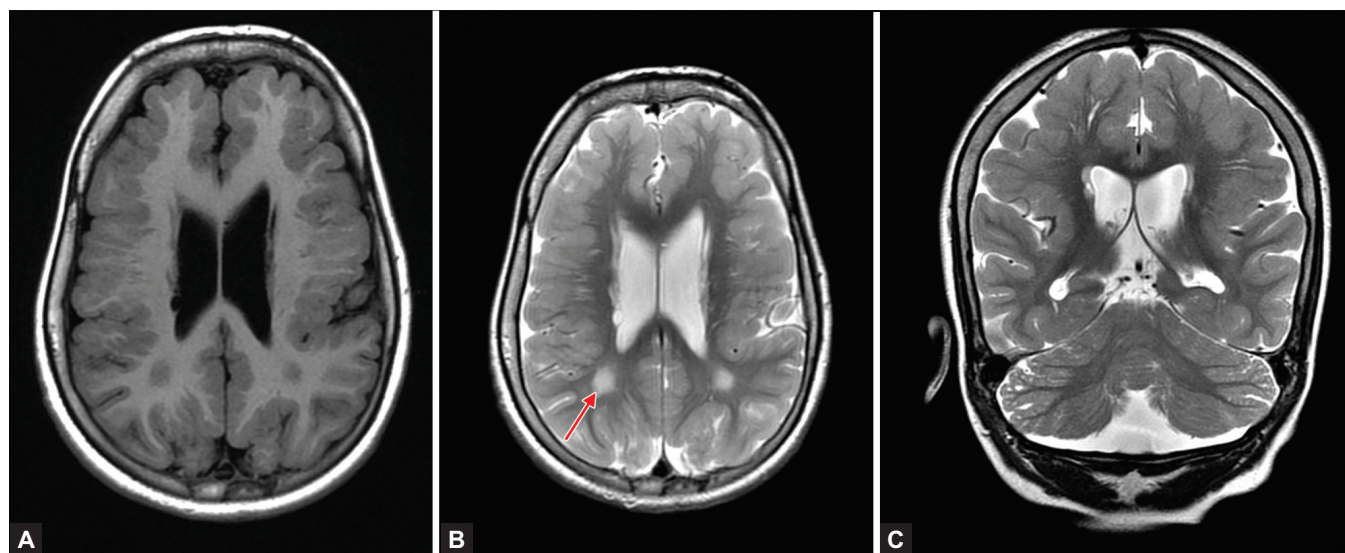
Figures 4A to C Fukuyama congenital muscular dystrophy. (A) Axial T1 and (B) T2-weighted images shows thickened, polymicrogyric cortex in the frontal lobes and perisylvian regions, with preserved cortical architecture in the temporal and occipital lobes. There are patchy foci of delayed myelination in the cerebral white matter. Coronal T2-weighted image (C) shows disorganized cerebellar cortex with small subcortical cysts

cerebral hemispheres and hypoplasia of the pyramidal tracts are the brain abnormalities seen in these patients. Severe cerebellar atrophy of the vermis and hemispheres, arachnoid cysts, and a hypoplastic brainstem are also the features in the posterior fossa. Meningocele or encephalocele is seen in 25% of patients. Common are microcephaly, ventricular dilation, and obstructive hydrocephalus **(Figs 5A to C)**.

CMD with mental retardation but no or mild structural brain abnormalities forms the intermediate form. In the mildest cases, presentation is with a LGMD phenotype (LGMD2K or LGMD 2N). Presentation is within the first decade with proximal weakness. The course is slowly progressive. Mild-to-moderate mental retardation is present, while only mild or no structural brain abnormalities have been described. It appears that most if not all patients with *POMT1* mutations have either structural or functional brain disease. This is not true for the mildest cases with mutations in *fukutin*, *FKRP*, and *POMGnT1* in which mild cases may have no structural or functional brain defects. α-dystroglycan staining, mutations in *POMT1* were the most frequent (25–40%) cause of alpha dystroglycanopathy.

Some specific gene defects that lead to abnormal glycosylation of alpha-dystroglycans and have variable clinical presentation have been described:

FKRP (Fukutin Related Protein)
Congenital Muscular Dystrophy

Spectrum of disease phenotypes is varied ranging from in-utero or lethal Walker-Warburg syndrome or muscle-eye-brain disease to intermediate forms (CMD with cerebellar involvement and CMD with mental retardation and microcephaly) to a mild limb-girdle muscular dystrophy phenotype. Associated brain manifestations are pontocerebellar hypoplasia, cerebellar cysts, agyria, thick frontal cortex, myopia, and retinal detachment. Dystrophy with mild mental retardation and cerebellar cysts has been described. An intermediate form is similar to congenital muscular dystrophy due to laminin-α2 mutations. In addition to hypotonia and weakness at birth and delayed motor milestones, hypertrophy of the legs and tongue is noted. Atrophy of proximal muscles and facial weakness are usually present with dilated cardiomyopathy and normal intelligence and brain imaging.

Milder cases present with a limb-girdle phenotype and are allelic with limb-girdle muscular dystrophy type 2I. Age at presentation varies from first year to the teens to mid adulthood. Scoliosis and ankle contractures similar to those of Duchenne muscular dystrophy with loss of ambulation occurring in the teens can also be seen. Muscle and tongue hypertrophy is common. Facial weakness is often present. Respiratory failure in the second decade often leads to death or the need for ventilatory assistance. With onset in the teens or adulthood, ambulation can be preserved until the sixth or seventh decade, but respiratory failure may develop before the sixth or seventh decade. Dilated cardiomyopathy develops in 50% of patients.

POMT1 and POMT2 Congenital Muscular Dystrophy

A wide spectrum of disease manifestation has been described, ranging from severe cases presenting as Walker-Warburg syndrome and mild cases presenting as a LGMD classified as LGMD2K (*POMT1*) and LGMD2N (*POMT2*). Severe cases have structural brain defects similar to those in Walker-Warburg syndrome or muscle-eye-brain disease.

CMD with mental retardation but no or mild structural brain abnormalities forms the intermediate form. Mildest cases present with LGMD phenotype (LGMD2K or LGMD 2N). They present within the first decade with proximal weakness. The course is slowly progressive. Mild-to-moderate MR is present. Most if not all patients with *POMT1* mutations have either structural or functional brain disease. This is not true for the mildest cases with mutations in *fukutin*, *FKRP*, and *POMGnT1* in which mild cases may have no structural or functional brain defects. Mutations in *POMT1* and POMT2 were the most frequent (25–40%) cause of alpha dystroglycanopathy.

LARGE Congenital Muscular Dystrophy

Mutations in the *LARGE* gene are the rarest cause of CMD with defect of α-dystroglycan glycosylation. Five cases were reported from 3 families. One case has been described in a 17-year-old female adolescent who presented with weakness and hypotonia at age 5 months. She had profound mental retardation and an MRI that showed mild white-matter abnormalities and structural malformations suggestive of aberrant neuronal migration.
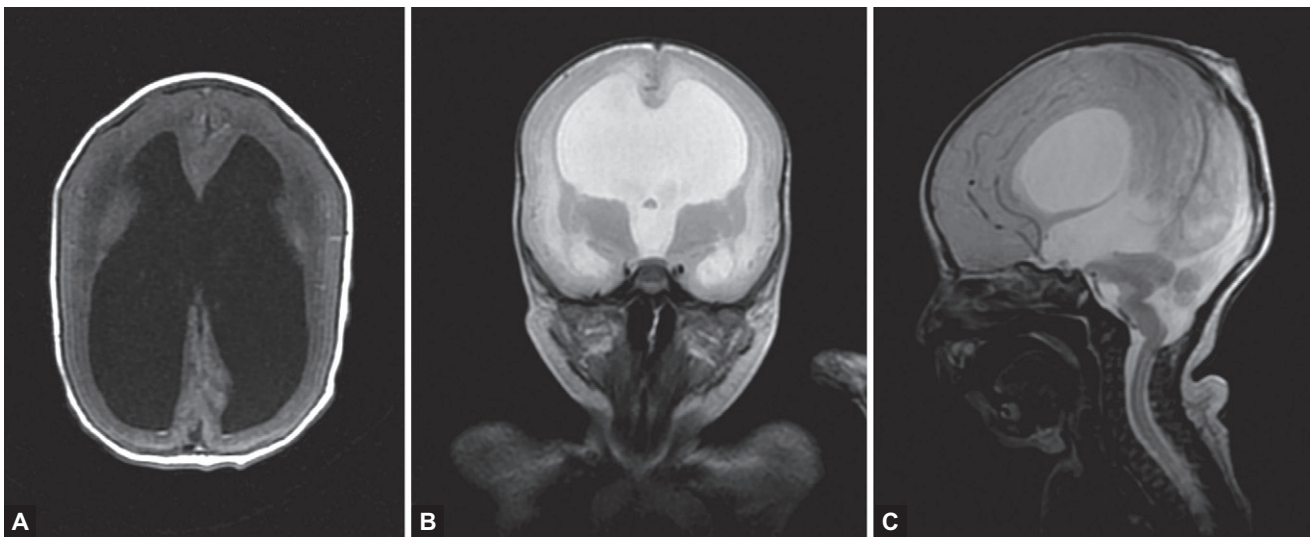
Figures 5A to C Walker-Warburg syndrome Axial T1 weighted (A) and coronal T2 weighted (B) images show gross hydrocephalus. The cortex shows absence of gyri and is lissencephalic. Sagittal T2 weighted image (C) shows hypoplasia and superior rotation of the cerebellar vermis. The brainstem is dysmorphic and shows a characteristic 's' shape. Also note the hypertrophic tectum and occipital encephalocele that are common association with this condition

An abnormal electroretinogram suggested eye abnormalities. Presentation was in the first year of life with hypotonia and delayed motor and cognitive milestones. They walked at 2 years, but with difficulty and muscle hypertrophy was noted. Mental retardation was present. Only mild eye abnormalities were noted, but severe abnormalities on brain MRI were seen including ventricular dilatation, cerebellar hypoplasia, high signal periventricular and deep white matter abnormalities, and in the more affected sibling pachygyria of the frontal lobes. Two siblings with consanguineous parents had a phenotype similar to Walker-Warburg syndrome and they died within 6 months CKs were markedly elevated. Both had eye abnormalities and brain imaging showing severe hydrocephalus and structural brain disease.

LMNA-deficient CMD (L-CMD)
The phenotype is caused by a mutation in the gene that encodes for proteins laminin A/C, also called LMNA. A wide variety of phenotypes including a CMD with rigid spine, Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, limb girdle muscular dystrophy, dilated cardiomyopathy, is caused by mutations in LMNA gene. Rarely neuropathies and dermal changes may also occur. LMNA-related CMD (L-CMD) also called as nuclear envelopathies, is part of the spectrum of laminopathies. L-CMD may present in the first six months of life as dropped head syndrome (absence of head or trunk support) or with progressive loss of head support after acquisition of sitting or walking ability. Hypotonia and weakness involves the axial-cervical muscles followed by more slowly progressive weakness of proximal upper limbs and distal lower limbs. Facial muscles are spared. With time, there is head lag, thoracic and lumbar spinal hyperextension (rigidity), lower limb contractures with no significant upper limb contractures and talipes equinovarus. Mechanical ventilation may be required before age two years in those more severely affected. L-CMD can be considered as an early-onset variant of Emery Dreifuss muscular dystrophy (EDMD) but they lack some of the typical early findings of EDMD, i.e., elbow contractures and major cardiac complications. They may develop in time. Genetic testing has identified a number of de novo dominant mutations.

Rare CMDs
A few rare disorders have been described with wide variety of clinical features related to different systems of the body along with musculoskeletal features of CMD. Some of these are as follows:

Integrin-alpha7 Deficiency
This rare disorder has been described in only a few children, who presented with hypotonia in infancy and delayed motor milestones (e.g., walked at age 2–3 years) mental retardation, contractures and respiratory failure.

CMD with Familial Junctional Epidermolysis Bullosa
Epidermolysis bullosa and muscular dystrophy first described in 1970s was subsequently described in several reports. The skin lesion include nail dystrophy, scalp alopecia and bullous lesions, which can be severe, even resulting in death and patients present with severe blistering often secondary to trauma or heat. Proximal muscle weakness is progressive often leading to wheelchair use by the second decade and may correlate with residual plectin function. Myasthenic syndrome has also been described with ptosis, ophthalmoplegia and facial weakness and may respond to pyridostigmine. Growth retardation, anemia, laryngeal webs, tooth decay, pyloric atresia, infantile respiratory insufficiency, and cardiomyopathy are the other systemic features. Presentation may then be as a late onset (20–40 years) muscular dystrophy. An LGMD syndrome without epidermolysis bullosa has been described as

presenting in early childhood with delayed walking. Proximal weakness eventually progresses and results in loss of ambulation.

CMD with Mitochondrial Structural Abnormalities
The defect in this phenotype is a mutation in the choline beta kinase gene. It is characterized by marked mental retardation microcephaly apart from hypotonia starting in early infancy and generalized muscle weakness. Some patients may have dilated cardiomyopathy and ichthyosiform skin changes.

DIFFERENTIAL DIAGNOSIS
Congenital muscular dystrophies need to be distinguished from other muscle diseases, anterior horn cell disease and central nervous system diseases with muscle weakness and low muscle tone:

Congenital Myopathies
X-linked myotubular myopathy, central core disease, centronuclear myopathy, and nemaline myopathy should be differentiated from CMD. Severity of presentation can range from decreased fetal movements or congenital floppy infant syndrome requiring mechanical ventilation to later-onset milder symptoms. Significant joint contracture is not a feature. Severe facial weakness or ophthalmoparesis seen in certain congenital myopathies is not found in the early stages of CMD, but may occur in the late stages of the subtype's laminin-α2 deficiency and the dystroglycanopathies. Congenital myopathy caused by RYR1 mutation can mimic SEPN1-related CMD with a clinical picture of multiminicore myopathy or a CMD-like presentation, with early onset hypotonia, axial weakness, and respiratory insufficiency. They typically have normal or near-normal serum CK concentration and histopathological evidence of developmental/structural muscle changes rather than dystrophic changes on muscle biopsy.

Limb-girdle Muscular Dystrophy
It is strictly the age of onset of muscle weakness in late childhood or adulthood that defines LGMD. The disease spectrum within the dystroglycanopathies ranges from congenital onset with or without CNS and eye involvement, to mild development delay, to a later-onset muscle weakness or limb-girdle muscular dystrophy with or without intellectual disability. Mutations in any of the six dystroglycanopathy-associated genes can result in CMD or LGMD. Similarly, the milder collagen VI-deficient myopathies can mimic LGMD.

Myotonic Dystrophy Type 1 (DM1)
This is an autosomal dominant multisystem disorder that affects skeletal muscle and smooth muscle as well as the eye, heart, endocrine system, and central nervous system; clinical severity of the phenotype ranges from mild to severe. Congenital DM1 is the severe early-onset form, characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common. Diagnosis is based on detection of an expansion of the GTC trinucleotide repeat in DMPK gene.

Pompe Disease (Glycogen Storage Disease Type II, GSD2, Acid Maltase Deficiency)
Hypotonia within the first few months of life, head lag, and marked cardiomegaly can also be a presenting manifestation of Pompe disease. Respiratory insufficiency in the first year can lead to frequent pulmonary infections. Other associated features include moderate hepatomegaly and macroglossia. Diagnosis is confirmed through identification of mutation in GAA, the gene encoding alpha-glucosidase (GAA), or by measuring deficient serum GAA

enzyme (also called acid maltase) activity. A later-onset phenotype may include nonprogressive or slowly progressive proximal muscle weakness, spinal stiffness without major limb contractures. Progressive respiratory failure results from diaphragmatic failure. This clinical picture may overlap with other congenital muscular dystrophies associated with rigid spine syndrome and particularly *SEPN1*-related CMD.

Congenital Onset of Facioscapulohumoral Muscular Dystrophy (FSHD)

It is characterized by congenital facial weakness, congenital deafness, mental retardation, and seizures. Facial weakness is the earliest and most prominent sign, distinguishing FSHD from CMD: Most children become wheelchair bound in childhood. Infantile FSHD may be inherited as a *de novo* mutation or in autosomal dominant fashion. FSHD is diagnosed by a molecular genetic test that identifies deletion of integral copies of a 3.3-kb DNA repeat motif, D4Z4, which is located in the subtelomeric region of chromosome 4q35.

Mitochondrial Myopathies

These have overlapping features including CNS involvement and are often associated with oculofacial involvement. Variability in weakness and fatigability is an important clinical clue. Overall, the diagnosis is based on specific morphological findings on biopsy, biochemical changes, and molecular genetic testing.

Spinal Muscular Atrophy (SMA)

It is an autosomal recessive disease characterized by progressive muscle weakness and atrophy. The onset of weakness ranges from before birth to adolescence or young adulthood. Diagnosis is based on electromyography showing neurogenic changes, histological findings of denervation atrophy on muscle biopsy and molecular genetic testing of *SMN1* and *SMN2 genes*, the two genes known to be associated with SMA.

Congenital Myasthenic Syndromes (CMS)

These are a group of neuromuscular junction disorders leading to weakness and fatigability and often respiratory and feeding complications. Arthrogryposis; club feet resulting from fetal immobility; bulbar, oculomotor, or facial involvement; diurnal variability of performance; and unexpected rapid failure in motor, respiratory, and/or feeding functions are typical clinical findings but are not always present. Electrophysiologic studies including EMG with repetitive nerve stimulation and stimulated single fiber EMG may identify abnormal neuromuscular transmission but are often difficult and require expertise.

Rigid Spine

The phenotype, early-onset muscle disease associated with rigid spine is caused by many disease states. The differential diagnosis are CMD type laminin-α2 deficiency (MDC1A), Bethlem myopathy, early onset CMD with cerebellar hypoplasia, congenital myopathies (centronuclear myopathy caused by mutations in *DNM2*, the gene which encodes dynamin 2, central core disease and multiminicore disease, caused by mutations in *RYR1*, the gene encoding skeletal muscle ryanodine receptor) and glycogen storage disease type II (i.e., Pompe disease).

Prader-Willi Syndrome (PWS)

It is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy by excessive eating and gradual development of morbid obesity unless externally controlled. Individuals with PWS have a distinctive behavioral phenotype. Hypogonadism is present in both males and females. The methylation-specific pattern of the PWS/AS region of chromosome 15q11 establishes the diagnosis in more than 99% of individuals.

Marinesco-Sjögren Syndrome (MSS)

It presents with cerebellar ataxia, early-onset cataracts, and mild to severe mental retardation, hypotonia, and muscle weakness. Serum CK is two to four times normal. Diagnosis is confirmed by clinical picture, brain MRI cerebellar atrophy, electron microscopic changes (autophagic vacuoles, membranous whorls, and electron-dense double membrane structures associated with nuclei) on muscle biopsy, and molecular genetic testing of *SIL1*, the only gene known to be associated with MSS. It is inheritance as an autosomal recessive disorder.

DIAGNOSIS OF CMD SUBTYPES

Diagnosis of subtypes of CMD usually involves medical history, family history, physical examination, neurologic examination, eye examination by a pediatric ophthalmologist, serum CK concentration, neuroimaging, muscle imaging, muscle and/or skin biopsy for histologic examination and immunohistochemistry, and molecular genetic testing **(Flow chart 1)**.

Clinical Evaluation

Medical History

In infants, medical history focusing on fetal movement, perinatal history, acquisition of milestones, feeding ability and respiratory complications, such as aspiration because of poor cry and poor cough should be carried out. In older children, history of cognitive abilities, motor abilities, muscle weakness, disease progression, joint contractures, scoliosis and spinal deformities, nutritional status, signs of respiratory compromise, hospitalizations, and infections should be elicited. There are some clues that may help identify the specific CMD subtype:

1. Congenital head lag as a result of marked cervicoaxial hypotonia associated with progressive cervical stiffness: *SEPN1*-related CMD
2. CNS involvement, psychomotor delay or intellectual disability: dystroglycanopathies; occasionally, laminin-α2 deficiency
3. Early signs of respiratory insufficiency:
   a. Very severe or progressive in the first two years of life: L-CMD; some very hypotonic infants with laminin-α2 deficiency
   b. Slowly progressive resulting in severe respiratory insufficiency in the first decade:
      i. *Nonambulatory*: Laminin-α2 deficiency; collagen VI-deficient CMD; L-CMD; dystroglycanopathy
      ii. *Ambulatory*: *SEPN1*-related CMD
4. Orthopedic complications:
   a. *Diffuse proximal and distal contractures and spinal stiffness and/or scoliosis*: Collagen VI-deficient CMD and laminin-α2 deficiency; late-stage L-CMD and dystroglycanopathies
   b. *Selective involvement of the spine*: *SEPN1*-related CMD; early in the course of laminin-α2 deficiency in children who are ambulatory; collagen VI-deficient CMD; L-CMD
5. *Joint deformities, torticollis or hip dislocation at birth*: Collagen VI-deficient CMD
6. *Rapidly progressive course with loss of head control*: L-CMD (dropped head syndrome)

Family History

Most of the CMD are inherited in an AR pattern. In the non-consanguineous, small nuclear families, often only one individual in a family with an AR disorder is affected. In contrast, most individuals with collagen VI-deficient CMD and all reported individuals with L-CMD have a de novo autosomal dominant mutation and therefore represent a single occurrence in a family.

Flow chart 1 Schematic evaluation of a child with hypotonia

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                        ┌─────────────────────┐
                        │    Floppy infant    │
                        └─────────────────────┘
                                  │
      ┌──────────────────────────────────────────────────────┐
      │ History, general physical examination, neurological  │
      │       and systemic examination (heart, liver, eyes)  │
      └──────────────────────────────────────────────────────┘
```

Floppy infant with normal strength:
• Hyper-reflexia
• Bilateral extensor plantars
• Global developmental delay
• Micro/macrocephaly
• Seizures

Cerebral causes:
• Hypoxic brain injury
• 21 trisomy
• Prader Willi syndrome
• Cerebral malformations
• **Zellweger** disease
• **Marinesco**-**Sjögren** syndrome

• Genetic analysis, karyotyping, VLCFA
• CT/MRI brain

Floppy infant with weakness (Lower motor neurone):
• Hypo/areflexia
• Delayed selective motor milestones
• Normal head size
• Severe proximal limb weakness
• Tongue fasciculations
• Feeble cry
• Myotonia (Congenital myotonic dystrophy)
• Paradoxical chest wall movement
• Ptosis, ophthalmoplegia, facial/bulbar paresis (CMS, congenital myopathy, mitochondrial)

• Joint contractures with distal hyperlaxity—collagen VI-deficient CMD
• Joint contractures without distal hyperlaxity—laminin alpha-2 deficiency
• Spinal stiffness without joint contractures—*SEPN1*-related CMD

CPK, RNS, NCS-EMG, MRI brain

• RNS (abnormal): congenital myasthenic syndromes
• NCS (abnormal) + EMG (normal): congenital hypomyelinating neuropathy
• NCS (normal) + EMG (abnormal):
    • Neurogenic-SMA
    • Myopathic-CMD, congenital myotonic dystrophy, congenital myopathies

Abnormal MRI brain—CMD
• Abnormal white matter changes not regressing with time—laminin alpha-2 deficiency

• Structural changes (including cobblestone appearance hydrocephalus, brainstem hypoplasia cerebellar cysts) or abnormalities in neuronal migration (lissencephaly or polymicrogyria) and white matter changes
• May regress with time—dystroglycanopathies

Appropriate genetic analysis based on above findings

If genetic analysis is inconclusive, then go for muscle biopsy with IHC

Physical Examination

Clinical clues include the following:

1. *Muscle pseudohypertrophy (calf and tongue)*: Dystroglycano-pathies (may resemble DMD).
2. *Diffuse joint contractures*: Laminin-α2 deficiency, collagen VI-deficient CMD.
3. *Distal hyperlaxity*: Collagen VI-deficient CMD.
4. *Hypertrophic scars or keloid formation*: Collagen VI-deficient CMD.
5. *Spinal stiffness without limb joint contractures: SEPN1-*related CMD.
6. *Axial hypotonia and weakness (poor trunk control) preceding spinal stiffness*: In early laminin-α2 deficiency, L-CMD, and collagen VI-deficient CMD.
7. *Cardiac involvement*: Rhythm disturbances in L-CMD; cardiomyopathy in dystroglycanopathies; right heart failure in any CMD subtype if chronic severe respiratory failure is untreated.
8. Nocturnal hypoventilation or respiratory failure in a person who is ambulatory: *SEPN1*-related CMD; occasionally collagen VI-deficient CMD.
9. The type and location of spinal deformity:
   a. Thoracic kyphosis: collagen VI-deficient CMD
   b. Thoracic lordosis: laminin-α2 deficiency, *SEPN1*-related CMD, and L-CMD; late stage of dystroglycanopathies. Lumbar hyperlordosis is frequently seen in all subtypes.
10. *Neurologic examination:* Features that may help in subtyping of specific CMD include:
    i. Head circumference: May be abnormal in laminin alpha 2 deficiency (macrocephaly) or in dystroglycanopathies (microcephaly or macrocephaly). Certain clinical findings can help direct one to the specific gene involved: microcephaly (*POMT1* and *POMT2);* macrocephaly and epilepsy (*POMGNT1);* cardiac involvement (*FKRP, FKTN, POMT1*)
    ii. CNS findings and abnormal white matter changes may be evident as:
        a. Pyramidal signs (hyper-reflexia, clonus) and cognitive involvement: dystroglycanopathies
        b. Seizures easy to control with routine antiepileptic drugs: typical for laminin-α2 deficiency
        c. Seizures refractory to polytherapy: often in MEB disease, especially those with *POMGNT1* mutations
        d. Intellectual disability associated with marked behavioral disturbances: suggestive of MEB disease, especially those with *POMGNT1* mutations.

Imaging

Neuroimaging MRI can guide diagnosis in CMD. The two CMD subtypes with abnormalities in brain imaging are laminin-α2 deficiency and the dystroglycanopathies.

1. In laminin-α2 deficiency abnormal white matter signal after age six months helps establish the diagnosis. White matter changes do not regress with time.
2. In the dystroglycanopathies, structural changes (including hydrocephalus, brainstem hypoplasia, cerebellar cysts) or abnormalities in neuronal migration (lissencephaly or polymicrogyria) are common. White matter changes may regress with time.

Muscle imaging Distinct recognizable patterns on muscle MRI in persons with spinal rigidity, normal merosin staining of skin or muscle biopsy, and normal serum CK levels can help differentiate between collagen VI-deficient CMD, *SEPN1*-related CMD, and L-CMD, and between the CMDs and the overlapping phenotypes considered in the differential diagnosis, caused by mutations in *RYR1*, *GAA* (encoding acid maltase) or *DNM2 genes.* Muscle MRI

can help differentiate muscular dystrophies with rigidity of the spine:

- *SEPN1:* There is selective involvement of the sartorius, and sparing of gastrocnemius
- *COL6A:* Bethlem myopathy patients had concentric atrophy and peripheral involvement, most clearly seen in vasti and gastrocnemius
- *COL6A:* Ullrich congenital muscular dystrophy (UCMD) patients had diffuse involvement of thigh muscles with selective sparing of anteromedial thigh muscles; more diffuse than Bethlem myopathy, but similar peripheral involvement of gastrocnemius
- *LMNA:* There is involvement of vasti at thigh level, medial > lateral gastrocnemius, and soleus muscle
- *LGMD2A (CAPN3):* Selective involvement of adductor magnus and posterior thigh muscles, medial > lateral gastrocnemius and soleus muscle.

Laboratory Evaluation

Serum CK levels In general CMD subtypes with positive merosin expression (collagen VI-deficient CMD, *SEPN1*-related CMD, L-CMD) show normal or mildly increased serum concentration of CK, while those with primary merosin deficiency (laminin-α2 deficiency) or secondary merosin deficiency (dystroglycanopathies) have high serum concentration of CK (> 4x normal values). In patients with congenital muscular dystrophy with familial junctional epidermolysis bullosa CK levels are usually more than 1000 IU/L.

Molecular genetic testing There is a trend recently to perform molecular genetic testing without muscle biopsy. This is due to the expanding role of molecular genetic testing in confirming the diagnosis of a CMD subtype. This is usually done, when the medical history, physical examination, and neurologic examination support the diagnosis of a CMD and a single gene defect is suspected as in laminin-α2 deficiency. In contrast, when multiple genes may need to be tested, as in the confirmation of the diagnosis of a dystroglycanopathy, performing immunohistochemical analysis of a muscle biopsy may identify the subtype prior to proceeding with molecular genetic testing. Two approaches can be followed: sequential molecular genetic testing or multigene testing. Once the disease-causing mutations are identified, molecular genetic testing of the parents is needed to clarify mode of inheritance and to provide accurate recurrence risk information to family members.

Muscle biopsy Histology typically shows a dystrophic or myopathic nonspecific pattern that does not suggest a congenital myopathy, mitochondrial disorder, or denervating disorder. The most significant dystrophic features are fiber size variability, presence of increased endomysial fibrosis, and variably necrotic and/or regenerative fibers **(Fig. 3)**. In some individuals with CMD, muscle biopsy may only show fiber size variation with absence of or only mild manifestations of fibrosis, necrosis, or regeneration. Inflammation may or may not be present. A muscle biopsy may be indicated if the diagnosis based on clinical examination remains unclear or molecular genetic testing does not confirm a diagnosis.

Immunohistochemical staining of muscle and/or skin can in some instances confirm protein deficiencies that can establish or exclude the diagnosis of a CMD subtype or confirm molecular genetic testing. Immunostaining of muscle can detect deficiencies of the proteins laminin-α2 (merosin), collagen VI, and alpha dystroglycan. Immunostaining of skin can detect deficiencies of laminin-α2 and collagen VI (**Fig. 3**). Immunostaining is not diagnostic or specific in *SEPN1*-related CMD or L-CMD. Partial merosin deficiency may be primary or secondary (i.e., caused by mutation in *LAMA2*, encoding laminin-α2 or caused by mutation of one of the genes associated with the dystroglycanopathy respectively. Plectin immunostaining is reduced in muscle Z-lines and skin in CMD with familial junctional epidermolysis bullosa.

TREATMENT

There is no definitive treatment for CMD. However, a multidisciplinary medical care improves quality of life and longevity in these patients. Management should be tailored to each individual, their CMD subtype, and rate of progression.

Assessment of respiratory function It is done with baseline lung function tests, including forced vital capacity in sitting and supine positions and blood gas analysis. Respiratory aids are provided to those with respiratory insufficiency and these include assisted cough and hyperinsufflation devices, Percussionaire, noninvasive ventilatory support, or mechanical ventilation via tracheostomy and chest physiotherapy.

Polysomnography This is to identify individuals with nocturnal hypoventilation and to evaluate individuals with symptoms of hypercapnea. This also helps in deciding about the requirement of ventilator support.

Assessment of muscle power Assessment of muscle power and joint contractures should be done by an occupational therapist and physical therapist.

Steroids In those who respond, the use of steroids appears to support prolonged ambulation. Assistance in education, and social and emotional support can improve the sense of social involvement and productivity and can reduce the sense of social isolation common in these patients.

Assessment of joint contractures and radiologic examination Assessment of joint contractures and spinal deformity should be done by orthopedic surgeon. Prevention of contractures and facilitate mobility by physical therapy and stretching exercises are helpful. Mechanical assistive devices including canes, walkers, orthotics, and wheelchairs can be used as needed to help ambulation and mobility. Posture in vertical, sitting, and supine positions is advised as improved posture may positively affect chest expansion.

Surgery Surgical intervention may be needed for orthopedic complications such as foot deformity, joint contractures, and scoliosis. Pros and cons of surgery for hip dislocation or joint contractures need to be considered in light of risk/benefit ratio.

Nutritional assessment and feeding Weight and height measurement, serum vitamin D and vitamin B12 levels, and calculation of body mass index should be done routinely. Most of the CMD patients have low body mass index and would require assisted feeding and nutritional supplements. Oral hygiene should also be taken care of.

Assessment of cardiac function It is required in all CMDs particularly those with dystroglycanopathy or L-CMD, with particular awareness that cardiomyopathy and/or arrhythmia can occur in the absence of severe muscle disease. Evaluation should also be done of secondary right heart failure and pulmonary hypertension in those with significant respiratory involvement.

Complete eye examination This should be done in all CMDs particularly in those with a dystroglycanopathy or if clinically indicated.

Speech therapy Several CMD patients require speech therapy due to involvement of brain and hypoventilation. Sometimes learning the use of gestures also helps in improving communication and quality of life.

PREVENTION

Prenatal testing and genetic counseling should be offered. Both molecular genetic testing and biochemical testing (for laminin-α2)

is possible if the disease-causing mutations in the family are known. Genetic status of the proband's parents decide the risk to the sibs of the proband. The risk to sibs is low, but greater than that of the general population if the disease-causing mutation found in the proband cannot be detected in the leukocyte DNA of either parent. This is because of the possibility of germline mosaicism. Carrier detection using molecular genetic techniques is possible if the disease-causing mutations in the family are known.

IN A NUTSHELL

1. CMD is a clinically and genetically heterogeneous group of inherited muscle disorders.
2. Muscle weakness typically presents from birth to early infancy. Affected infants typically appear *floppy* with hypotonia and poor movements.
3. Muscle weakness may improve, worsen, or stabilize in the short term; however, with time progressive weakness and joint contractures, spinal deformities, and respiratory compromise may affect quality of life and lifespan.
4. Mental retardation ranging from intellectual disability to mild cognitive delay, structural brain and/or eye abnormalities, and seizures are found almost exclusively in the dystroglycanopathies while white matter abnormalities without major cognitive involvement tend to be seen in the laminin-α2-deficient subtype.
5. The main CMD subtypes are: laminin-α2 (merosin) deficiency (MDC1A), collagen VI-deficient CMD, the dystroglycanopathies (caused by mutations in *POMT1, POMT2, FKTN, FKRP, LARGE, POMGNT1, and ISPD*), SEPN1-related CMD (previously known as rigid spine syndrome, *RSMD1*) and LMNA-related CMD (L-CMD). They are grouped by involved protein function and gene in which causative mutations occur.
6. The diagnosis of CMD relies on clinical findings, imaging of brain and muscle, muscle histology (dystrophic features without the structural changes seen in the congenital myopathies), immunohistochemistry of muscle and/or skin and molecular genetic testing.
7. There is no treatment till date.

MORE ON THIS TOPIC

Bönnemann CG. Congenital muscular dystrophy. In: Squire LR, ed. Encyclopedia of Neuroscience. Vol 3. Oxford, UK: Oxford Academic Press; 2009. pp. 67-74.

Briñas L, Richard P, Quijano-Roy, et al. Early onset collagen VI myopathies: Genetic and clinical correlations. Ann Neurol. 2010;68:511-20.

Geranmayeh F, Clement E, Feng LH, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. Neuromuscul Disord. 2010;20:241-50.

Godfrey C, Escolar D, Brockington M, et al. Fukutin gene mutations in steroid-responsive limb girdle muscular dystrophy. Ann Neurol. 2006;60:603-10.

Kirschner J, Bönnemann CG. The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. Arch Neurol. 2004;61:189-99.

Mercuri E, Clements E, Offiah A, et al. Muscle magnetic resonance imaging involvement in muscular dystrophies with rigidity of the spine. Ann Neurol. 2010;67:201-8.

Mercuri E, Messina S, Bruno C, et al. Congenital muscular dystrophies with defective glycosylation of dystroglycan: a population study. Neurology. 2009;72:1802-9.

Murakami T, Hayashi YK, Noguchi S, et al. Fukutin gene mutations cause dilated cardiomyopathy with minimal muscle weakness. Ann Neurol. 2006;60:597-602.

Sparks SE, Escolar DM. Congenital muscular dystrophies. Handb Clin Neurol. 2011;101:47-79.

Chapter 43.8
Congenital Myopathies

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The clinical categorization of congenital myopathies was first introduced by Shy and Magee in 1956. Congenital myopathies are defined by characteristic features observed on muscle biopsy, and the major subtypes include nemaline myopathy, core myopathy, centronuclear myopathy (CNM) and congenital fiber type disproportion (CFTD). Congenital myopathies are a clinically and genetically heterogeneous group of muscle diseases that typically present with hypotonia, motor delay, and muscle weakness. Onset is usually at birth or within the 1st year of life, though patients are diagnosed throughout all pediatric and adult periods. There is a large spectrum of severity, ranging from wheelchair and ventilator dependence to minimal weakness and exercise intolerance. Diagnosis is based on the findings from muscle biopsy, genetic testing, and family history. At present, no curative therapies have been developed, though many are under investigation. There are also few if any disease modifying treatments, and there is a great need for both better understanding and treatment for these often devastating disorders of skeletal muscle.

EPIDEMIOLOGY

Congenital myopathies are estimated at an overall prevalence of 1:22,480–1:26,000 among pediatric patients and 1:28,600–1:135,000 among a combined cohort of pediatric and adult patients. The prevalence of each subtype varies. In several studies, core myopathies were found to be the most prevalent at 1:150,000 for multiminicore disease and 1:249,000–1:170,000 for central core disease. A histopathologic review at the All India Institute of Medical Sciences also found that core myopathies were the most common diagnosis (24% central core disease and 20% multiminicore disease). In one study, the prevalence of CFTD was found to be 1:240,000 and 1:400,000 for CNMs. The prevalence of nemaline myopathy was estimated at 1:179,000–1:1,210,000. Few prevalence studies have been performed; therefore additional studies are needed to further confirm these results.

ETIOPATHOGENESIS

As described below, mutations causing congenital myopathy tend to be in genes associated with the process of muscle contraction, rather than in genes associated with myofiber energy metabolism, stabilization, or repair. The congenital myopathies are named for their histopathologic appearance—myopathies with protein accumulation, cores, central nuclei, and fiber size variation. There are five main subtypes within these groups: (1) nemaline myopathy (including cap disease and zebra body myopathy), (2) core-rod myopathy, (3) core myopathies (including central and multiminicore diseases), (4) CNMs (including myotubular and autosomal centronuclear myopathies), and (5) CFTD. Investigations of the function of genes mutated in congenital myopathies have led to an understanding that abnormalities in a subset of muscle structures and function are the main pathologic drivers of disease in congenital myopathies. In particular, core myopathies and CNMs are associated with abnormalities in the structure and function of the triad (the muscle structure that is responsible for excitation-contraction coupling) and nemaline myopathies are associated with abnormalities in the actin thin filament.

CLINICAL FEATURES

Congenital myopathies are a group of conditions characterized by hypotonia, weakness, and variable respiratory involvement. Onset is typically at birth and the clinical course is usually static or slowly progressive. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked. Mutations in 18 genes (exhibiting a variety of inheritance patterns within many of these genes) have been associated with multiple subtypes, exemplifying the genetic heterogeneity among these conditions **(Table 1)**.

Clinical Features Associated with Mutations in Specific Genes

When evaluating a child for a suspected diagnosis of congenital myopathy, there are pertinent clinical features that can guide the diagnostic process **(Table 2)**.

Findings associated with skeletal muscle function and metabolism The weakness seen in congenital myopathy can

Table 1 Classification of congenital myopathies

Subtype	Inheritance pattern	Genes
Nemaline myopathy (NM)	AD, AR	ACTA1
	AR	CFL2
	AD	KBTBD13
	AR	KLHL40
	AR	KLHL41
	AR	NEB
	AR	RYR1
	AR	TNNT1
	AD	TPM2
	AD, AR	TPM3
Cap disease (NM Variant)	AD	ACTA1
	AD	TPM2
	AD	TPM3
Zebra body myopathy (NM Variant)	AD	ACTA1
Myosin storage myopathy (hyaline body myopathy)	AD	MYH7
Core-rod myopathy	AD	KBTBD13
	AR	NEB
	AD, AR	RYR1
Central core disease	AD, AR	RYR1
Multiminicore disease	AR	RYR1
	AR	SEPN1
Centronuclear myopathy	AR	BIN1
	AD	CCDC78
	AD	DNM2
	XL	MTM1
	AD	MYF6
	AR	RYR1
	AR	TTN
Congenital fiber type disproportion	AD	ACTA1
	AD	MYH7
	AR	RYR1
	AR	SEPN1
	AD	TPM2
	AD	TPM3

Congenital myopathy subtypes can be further defined by inheritance pattern (AD = autosomal dominant, AR = autosomal recessive, or XL = X-linked) and gene mutation.
Source: Adapted from Jones HR Jr, DeVivo DC, Darras BT (eds). Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach, 1st ed. United States of America: Elsevier; 2014.

Table 2 Key clinical features of congenital myopathy subtypes

Feature	Genetic subtype
Distal muscle weakness	DNM2, MYH7, NEB, TPM2, TPM3
Prominent neck extension weakness (dropped head syndrome)	SEPN1
Malignant hyperthermia	RYR1, STAC3
Exercise induced myalgias	DNM2, RYR1
Orthopedic issues	
Severe arthrogryposis/fetal akinesia	ACTA1, KLHL40, NEB, RYR1, TPM2
Congenital dislocation of the hips	RYR1
Prominent scoliosis	NEB, RYR1, SEPN1
Rigid spine	RYR1, SEPN1
Ophthalmoparesis +/- ptosis	DNM2, MTM1, RYR1
Lower facial weakness/marked bulbar involvement	DNM2, MTM1, NEB, RYR1
Respiratory involvement	
Present at birth	ACTA1, MTM1
Moderate	BIN1, DNM2, RYR1
Out of proportion to muscle weakness	ACTA1, DNM2, MTM1, NEB, SEPN1, TPM3
Cardiomyopathy	ACTA1, DNM2, MYH7, TPM2, TTN
Undescended testes	MTM1, RYR1
Macrosomia	MTM1
Bleeding diathesis, liver, and gastrointestinal complications	MTM1

The presence of specific clinical features can guide genetic testing.

be extremely variable with respect to severity and distribution. While most congenital myopathies present with proximal muscle weakness, predominant distal muscle involvement (as is more typically seen in neuropathies) can been seen with mutations in *DNM2, MYH7, NEB, TPM2,* and *TPM3.* Prominent neck extension weakness (also called dropped head syndrome) is suggestive of a mutation in *SEPN1.* Susceptibility to malignant hyperthermia is an important consideration in some neuromuscular diseases. Malignant hyperthermia is a hypermetabolic response to certain inhaled anesthetics and/or depolarizing muscle relaxants. Among patients with congenital myopathies, a clear association has been linked with mutations in *RYR1* and *STAC3.* Exercise-induced myalgias have been reported in patients with *DNM2* and *RYR1* mutations.

Orthopedic findings Orthopedic issues are a common complaint among patients with congenital myopathies due to a combination of insufficient movement during development and insufficient muscle traction during postnatal skeletal growth. Severe arthrogryposis has been associated with mutations in *ACTA1, KLHL40, NEB, RYR1,* and *TPM2.* Congenital dislocation of the hips (*RYR1*), prominent scoliosis (*NEB, RYR1,* and *SEPN1),* and spinal rigidity *(RYR1* and *SEPN1)* can be suggestive of mutations in specific genes. Patients with *SEPN1* mutations typically develop spinal rigidity prior to scoliosis.

Facial features The "myopathic facies" associated with congenital myopathy is characterized by a long narrow face and open mouth. These facies are reflections of skeletal muscle

weakness during development and growth, and should not be considered deformations or malformations in the classic sense. Ophthalmoparesis, which may be accompanied by ptosis, is suggestive of CNM and/or of mutations in *DNM2, MTM1,* and *RYR1.* Lower facial weakness and bulbar symptoms are seen with most histopathologic subtypes but is often profound in the setting of nemaline myopathy.

Respiratory findings Variable respiratory involvement has been reported across all subtypes. However, onset and severity may provide guidance on further diagnostics. Severe (*ACTA1* and *MTM1*) or moderate *(RYR1, DNM2,* and *BIN1)* respiratory involvement may suggest specific genes. Some patients present with respiratory involvement out of proportion to muscle weakness; this is suggestive particularly of mutations in *SEPN1,* but can also been observed with *NEB, ACTA1,* and *TPM3.*

Cardiac findings While cardiomyopathy is rarely associated with congenital myopathies, it has been reported in patients with *ACTA1, DNM2, MYH7, TPM2,* and, most commonly, with *TTN* mutations. It is important to distinguish those with primary cardiomyopathy versus secondary cardiomyopathy (i.e., cor pulmonale) due to marked respiratory involvement; the latter has historically been described with *SEPN1* mutations.

Other findings Undescended testes have associated with mutations in *MTM1* and *RYR1.* Macrosomia (length above the 90th percentile and large head circumference) is suggestive of mutations in *MTM1.* Bleeding diathesis and liver and gastrointestinal complications have been reported among some patients with myotubular myopathy (MTM) and *MTM1* mutations.

DIFFERENTIAL DIAGNOSIS

There are some key clinical findings that suggest diagnoses other than a congenital myopathy. Increased deep tendon reflexes and/or central nervous system abnormalities are not typically seen in congenital myopathy. That being said, it is important to distinguish primary central nervous system disease from situations where acquired hypoxic ischemic injury has occurred due to respiratory failure from a congenital myopathy. Tongue fasciculations are suggestive of a diagnosis of spinal muscular atrophy (SMA); SMA can have many overlapping clinical features with congenital myopathies, including proximal extremity muscle weakness and reduced/absent reflexes. Dysmorphic features are not typically associated with the congenital myopathies with the exception of King-Denborough syndrome and Native American myopathy. Metabolic abnormalities such as increased lactate or metabolic acidosis are not typically associated with the congenital myopathies. Joint laxity can occur in many patients with congenital myopathies, but if extreme laxity is noted, a diagnosis of a collagen VI myopathy should be considered. There are many overlapping clinical features between congenital myopathies and congenital myotonic dystrophy (cDM1). Genetic testing for cDM1 should always be considered when neonatal hypotonia and weakness are observed, as it is the key alternative diagnosis for congenital myopathies. Of note, mothers of infants with cDM1 may be asymptomatic, but should carry an expanded triplet repeat in the *DMPK* gene.

APPROACH TO DIAGNOSIS

Creatine Kinase

Creatine kinase (CK) is typically normal or mildly elevated (2–3x normal), a distinguishing feature from the congenital muscular dystrophies. However, in some subtypes such as *RYR1*-related myopathies, CK and muscle biopsy may be suggestive of a dystrophic process.

Electromyography/Nerve Conduction Velocities

Electromyography (EMG) will likely show myopathic changes and nerve conduction velocities (NCVs) should be normal, ruling out a neuropathy as a major cause of weakness. Repetitive stimulation [compound muscle action potential (CMAP)] and single fiber EMG are helpful to diagnose and/or distinguish a congenital myasthenic syndrome but may also be useful to identify neuromuscular junction abnormalities in some forms of CNM (*MTM1* and *DNM2*). In these cases, individuals may have the electrodiagnostic features of a myasthenic syndrome and may respond to acetylcholinesterase inhibitors.

Muscle Biopsy

Muscle biopsy provides the diagnostic standard for congenital myopathies, as these disorders are characterized by specific structural abnormalities. It is important to choose the correct muscle to biopsy, as muscles that are unaffected may lack histopathologic features consistent with the diagnosis and end stage muscle may contain mostly fat. Muscle ultrasound or MRI (described below) can be useful to guide the selection of an appropriate muscle to biopsy.

Specific pathological findings on muscle biopsy may narrow down the diagnosis to a group of subtypes and some findings may guide specific genetic testing. It is important to note that while pathological features can guide genetic testing, not all features listed in **Table 3** will be present in every patient.

Nemaline Myopathy

Nemaline myopathy is diagnosed by observing the presence of cytoplasmic protein aggregates called nemaline rods or bodies **(Fig. 1)**. These structures are best identified on modified Gomori trichrome staining and should be confirmed by electron

Table 3 Distinguishing features of congenital myopathies on muscle biopsy

Feature	Genetic subtype
Rods (nemaline bodies)	*ACTA1, CFL2, KBTBD13, KLHL40, KLHL4, NEB, RYR1, TNNT1, TPM2, TPM3*
Rods confined to type I fibers	*TPM3*
Intranuclear rods	*ACTA1*
Caps	*ACTA1, TPM2, TPM3*
Zebra bodies	*ACTA1*
Hyaline bodies	*MYH7*
Cores	*MYH7, RYR1, SEPN1*
Central cores	*RYR1*
Minicores	*RYR1, SEPN1*
Cores and rods	*KBTBD13, NEB, RYR1*
Central nuclei	*BIN1, CCDC78, DNM2, MTM1, MYF6, RYR1, TTN*
Marked myofiber atrophy and large central aggregates of mitochondria and glycogen	*MTM1*
Radial strands	*DNM2*
Necklace fibers	*MTM1, DNM2*
Fiber type disproportion	*ACTA1, MYH7, RYR1, SEPN1, TPM2, TPM3*
Marked type I fiber predominance (>90%)	*RYR1*

The presence of specific pathological features can guide genetic testing.
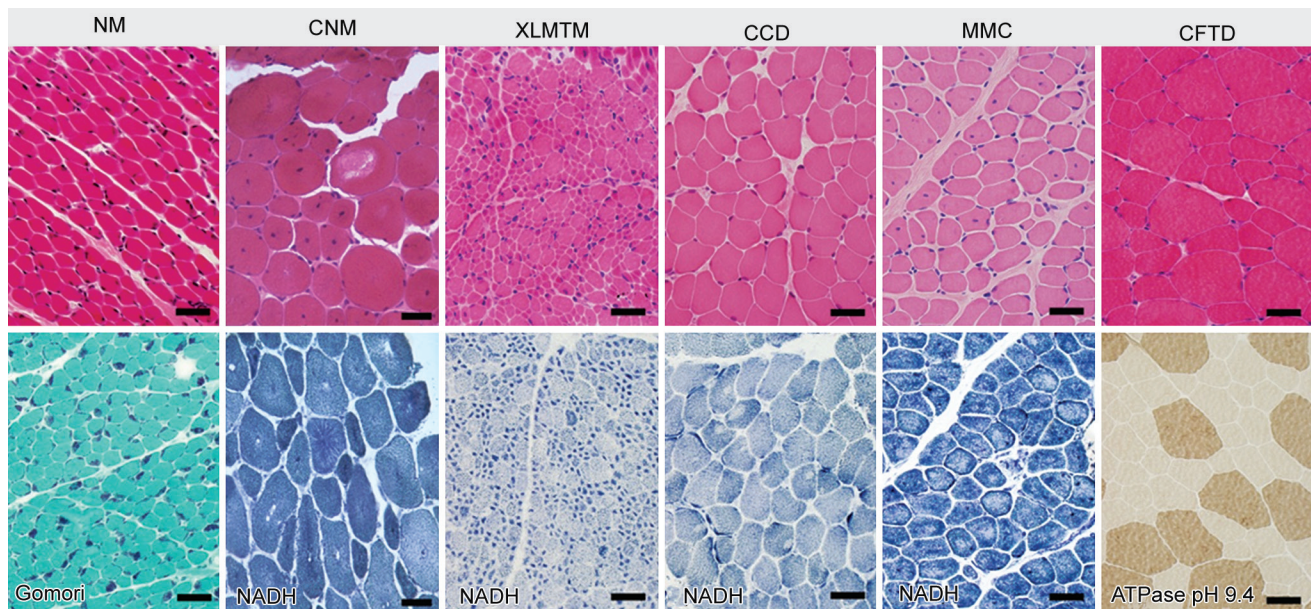
Figure 1 Pathological findings on muscle biopsy in congenital myopathy. The characteristic pathology of nemaline myopathy (NM), centronuclear myopathy due to *DNM2* mutation (CNM), X-linked myotubular myopathy (XLMTM), central core disease (CCD), multiminicore disease (MMC) and congenital fiber type disproportion (CFTD) are shown. The top row of images all shows staining with hematoxylin and eosin (H&E). Special stains related to the diagnosis of each disease are shown in the bottom row of images, including Gomori trichrome (Gomori), NADH, and an ATPase stain performed at pH 9.4 (which stains the type 2 fibers darkly and the type 1 fibers lightly). Bar = 40 μm

microscopy (EM), if possible. The number of rods and percentage of fibers with rods do not correlate with disease severity, and a variety of abnormalities of contractile function (including altered thin filament length and abnormal calcium utilization) and variable degrees of myofiber smallness (hypotrophy) have been found in muscles harboring nemaline myopathy. Nemaline myopathy is caused by mutations in at least 10 genes, many of which encode the sarcomeric thin filament **(Table 1)**. Nemaline rod distributions in certain configurations can be suggestive of causative genes, including *TPM3* (rods and hypotrophy only seen in type 1 myofibers), *ACTA1* (intranuclear rods), and *TPM2* (cap-shaped subsarcolemmal aggregates of rod-like material). Some nemaline rod/body variants, such as zebra bodies composed of stacks of thin filament material, can be seen and suggest an *ACTA1* gene mutation.

Core Myopathies

Cores are areas devoid of mitochondria and therefore, lack oxidative enzyme activity **(Fig. 1)**. These areas are frequently associated with condensed areas of contractile apparatus, so they often retain their myosin ATPase reactivity. Central cores and minicores are best identified on oxidative stains, nicotinamide adenine dinucleotide dehydrogenase (NADH) and succinate dehydrogenase (SDH). As there is considerable genetic overlap between the *RYR1* and *SEPN1* mutations that cause central core and multiminicore disease, the pathological distinction between these structures is no longer as critical as it once seemed. Central cores are large, single structures that are longer than they are wide, and minicores are usually smaller structures that only span a few sarcomeres and in which several can be seen in a single transversely-sectioned myofiber. Cores may look similar to targetoid lesions (typically a neurogenic finding) or areas of reduced staining (central pallor), therefore it is important to confirm with EM when possible. Some cases of core myopathy due to *RYR1* mutations can show an exceptional degree of type 1 fiber predominance (> 90%).

Core-Rod Myopathy

Core-rod myopathy is characterized by the presence of both cores and rods on biopsy. EM is vital to confirm the presence of both rods and cores, especially given that nemaline rod aggregates may displace mitochondria to provide the appearance of cores on oxidative stains.

Centronuclear Myopathies

It is important to distinguish central nuclei from internalized nuclei. Internalized nuclei are typically associated with regenerating/regenerated myofibers, myotonic dystrophy, or even normal fibers in the area of a myotendinous insertion site. The relevance of central nucleation to the production of weakness is debatable and it is potentially just an easily recognizable indication of organelle mislocalization that is frequently observed in these diseases. Myofiber hypotrophy and disorganization and loss of triad structures on EM also occur to varying degrees across the several genetic causes of CNM. The clinical history and pattern of organelle mislocalization can be very useful in identifying the causative gene. A severe neonatal phenotype with marked myofiber smallness and large central aggregates of mitochondria and glycogen strongly suggests an *MTM1* mutation. In contrast, a less severe phenotype and the presence of radial strands (spokes on a wheel) on oxidative stains and/or PAS are suggestive of a *DNM2* mutation. Necklace fibers (rings of mitochondria and glycogen connecting to an internalized nucleus) have been identified in some cases of CNM. These may be suggestive of a female carrier of an *MTM1* mutation, late-onset MTM in males, or *DNM2* mutations.

Congenital Fiber Type Disproportion

Congenital fiber type disproportion represents a specific pattern of myofiber hypotrophy that can be seen across the entire range of congenital myopathy **(Fig. 1)**, and includes moderate to severe hypotrophy of type 1 fibers in the biopsy (type 1 fibers > 25% smaller than type 2 fibers), often occurring in combination with type 1 fiber predominance (>55% of fibers are type 1 fibers). The presence of this pattern in association with nemaline rods, excessive central nucleation, or core structures would yield diagnoses of nemaline myopathy, CNM, and core myopathy, respectively. When these specific structures are not present, however, this pattern of hypotrophy is diagnosed as CFTD. Some patients with CFTD may later be re-classified as other congenital myopathies due to the presence of additional pathological findings on repeat biopsies. The presence of CFTD pathology without additional pathological findings is most commonly associated with mutations in *TPM3*. Particularly marked fiber type disproportion (>90% type 1 fibers) has been seen with mutations in *RYR1*.

Muscle MRI

Muscle MRI is a noninvasive method for identifying affected muscle groups. The procedure is relatively quick and well tolerated by many children, and most do not require anesthesia for the procedure. MRI can identify patterns of affected muscle groups associated with specific gene mutations **(Table 4)**. According to Quijano-Roy and colleagues (2011), proximal versus distal weakness and the involvement or sparing of the tibialis anterior and soleus are the most helpful in guiding genetic diagnosis. Even if a specific pattern is not identified, muscle MRI can help guide the site for muscle biopsy. It is important to biopsy a muscle that is affected, but not end stage.

Muscle Ultrasound

Muscle ultrasound is another method that may guide genetic testing using patterns of muscle involvement and selection of muscle for biopsy. Similar patterns as to what can be observed with MRI are seen with ultrasound. However, the procedure is highly dependent on ultrasonographer's expertise.

Genetic Testing

Specific clinical features and/or results of muscle MRI and/or biopsy may guide genetic testing selection **(Tables 2 to 4)**. If there are specific or diagnostic findings, single gene sequencing (Sanger and/or next generation) may be the most cost-efficient method for confirming the diagnosis. However, most often the clinical picture and muscle biopsy do not point to a single genetic cause, or patients may want to avoid an invasive procedure such as a muscle biopsy. Therefore, the most cost effective and least invasive diagnostic testing strategy may be a congenital myopathy next generation sequencing (NGS) gene panel. Several panels are currently available clinically by multiple companies. There are several considerations when choosing a panel: (1) Mutation type, (2) gene coverage, and (3) pricing. It is important to consider whether the testing includes parental testing of variants of unknown significance, Sanger confirmation of variants identified and/or areas of low coverage are backfilled with Sanger sequencing, and deletion/duplication testing.

Recent publications point to some of the drawbacks of NGS panels in diagnosing neuromuscular disorders. NGS can detect sequence variations and small insertions/deletions (indels), however, it cannot detect repeat expansions or complex structural variants. Additionally, some areas have consistently low coverage (typically < 20X) due to sequence complexity, problematic library synthesis, and unusual GC content. Valencia and colleagues

Table 4 Lower extremity muscle MRI findings in congenital myopathy subtypes

Gene	Muscles																			
	AL	AM	BF	GSL	GSM	GMa	GMi	GRA	PER	PT	PTB	RF	SAT	SMM	ST	SOL	TA	VIM	VL	VM
ACATA1	S	A				A		S	A			S	A		A		A			
BIN1			S	A				A			S					S	A			
DNM2	A		A	A		A		S		S			S	A		A		A		
MTM1	S	A						S		A		S								A
MYH7					S			A								A	A			
NEB					A						S					A	A			
RYR1		A				A		S				S	A				A		A	
SEPN1	S			A	A			S		A		S	A							
TPM2		A	A					S				S	S	A						

The pattern of affected muscles on MRI can guide genetic testing.

Abbreviations: A, affected; S, spared; AL, adductor longus; AM, adductor magnus; BF, biceps femoris; GSL, lateral gastrocnemius; GSM, medial gastrocnemius; GMa, gluteus maximus; GMi, gluteus minimus; GRA, gracilis; PER, peroneal; PT, posterior thigh; PTB, posterior tibialis; RF, rectus femoris; SAT, sartorius; SMM, semimembranosus; ST, semitendinosus; SOL, soleus; TA, tibialis anterior; VIM, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

Source: Adapted from Jones HR Jr, DeVivo DC, Darras BT (eds). Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 1st ed. United States of America: Elsevier; 2014.

(2013) identified multiple genes (*COL6A1, COL6A2, COL6A3, FKTN, ITGA7, LAMA2, POMT1, POMT2, SEPN1*) with consistently low coverage using a congenital muscular dystrophy NGS panel. NGS also has a high error rate compared to Sanger sequencing. Artificial mutations are produced during template amplification or sequencing. Therefore, all variants identified by NGS must be confirmed by Sanger sequencing. Lastly, panels identify variants of unknown significance in genes that may not have otherwise been tested. It is important to interpret variants in the context of the patient's phenotype. It may be helpful to compare the variant to published mutation types and location to help in predicting the pathogenicity of the variant.

MANAGEMENT

Medical management of patients with congenital myopathies should include a multidisciplinary team including the following specialties: neurology, pulmonology, orthopedics, rehabilitation specialists, gastrointestinal/nutrition, and genetics. Depending on the specific subtype, ophthalmology and cardiology may need to be involved. Details of specific standard of care guidelines can be found in the publication by Wang and colleagues (2012).

Specific management guidelines are available for some subtypes. For nemaline and centronuclear myopathies, speech, feeding, and secretion management will be needed. Additionally, many patients with nemaline and centronuclear myopathies may need respiratory support, in particular patients with *ACTA1, BIN1, DNM2, MTM1, NEB, RYR1,* and *TPM3* mutations. Respiratory management will be particularly important for patients with *SEPN1* mutations. CNM patients with ptosis may benefit from surgical management. Orthopedic management of scoliosis will be important for patients with *NEB, RYR1,* and *SEPN1* mutations. Cardiac screening should be initiated in patients with *ACTA1, DNM2, MYH7, TPM2,* and *TTN.* Malignant hyperthermia precautions are needed for patients with *RYR1* mutations.

No curative therapies are currently available for the congenital myopathies; however, several therapies are under investigation. These include L-tyrosine for nemaline myopathy. L-tyrosine may improve bulbar function, energy levels, and exercise tolerance. Neuromuscular junction abnormalities have been identified in animal models and patients with CNM/MTM and treatment with an acetylcholinesterase inhibitor, such as Mestinon, has

been reported to improve some symptoms. Gene and enzyme replacement therapies are currently being developed for patients with MTM. Oxidative stress has been identified in *SEPN1* and *RYR1*-related myopathies. Treatment with antioxidants, such as N-acetylcysteine (NAC), has reduced oxidative stress in animal models and patient myotubes. Clinical trials for both myopathies using NAC treatment are currently underway. Additional therapies are under investigation for many congenital myopathy subtypes.

IN A NUTSHELL

1. Key clinical features and diagnostic testing results can narrow the differential for congenital myopathy subtypes.
2. Specific management guidelines should be considered when treating patients with different subtypes.

MORE ON THIS TOPIC

Amburgey K, McNamara N, Bennett LR, et al. Prevalence of congenital myopathies in a representative pediatric United States population. Ann Neurol. 2011;70:662-5.

Dubowitz V, Sewry C. Congenital Myopathies and Related Disorders. China: Saunders Elsevier; 2013.

Iannaccone ST, Castro D. Congenital muscular dystrophies and congenital myopathies. Continuum (Minneap Minn). 2013;19:1509-34.

North KN, Wang CH, Clarke N, et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord. 2014;24:97-116.

North KN, Goebbel H. Congenital myopathies. In: Jones HR Jr, DeVivo D, Darras B. Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 1st ed. United States of America: Elsevier; 2014. pp. 601-32.

Quijano-Roy S, Carlier RY, Fischer D. Muscle imaging in congenital myopathies. Semin Pediatr Neurol. 2011;18:221-9.

Uppin MS, Meena AK, Sundaram C. Spectrum of congenital myopathies: a single centre experience. Neurol India. 2013;61:254-9.

Valencia CA, Ankala A, Rhodenizer D, et al. Comprehensive mutation analysis for congenital muscular dystrophy: a clinical PCR-based enrichment and next-generation sequencing panel. PLoS One. 2013;8:e53083.

Vasli N, Laporte J. Impacts of massively parallel sequencing for genetic diagnosis of neuromuscular disorders. Acta Neuropathol. 2013;125:173-85.

Wang CH, Dowling JJ, North K, et al. Consensus statement on standard of care for congenital myopathies. J Child Neurol. 2012;27:363-82.

Chapter 43.9
Neuromuscular Transmission Disorders
Venkateswaran Ramesh

PHYSIOLOGY OF NORMAL NEUROMUSCULAR TRANSMISSION

Depolarization in a motor neuron results in propagation of action potentials to the motor end-plate. This triggers opening of voltage-gated calcium channels in the presynaptic membrane terminals, which in turn triggers release of the chemical neurotransmitter acetylcholine. Acetylcholine diffuses across the synaptic cleft and binds to receptors at the postsynaptic membrane, giving rise to end-plate potentials via opening of sodium channels in the skeletal muscle membrane. The amplitude of the end-plate potential must exceed a critical threshold in order to cause depolarization of the skeletal muscle cell and contraction of the myocyte. A nerve impulse causing release of a large number of quanta of acetylcholine can induce depolarization of a large number of myocytes in the motor unit, which summate to generate a compound muscle action potential (CMAP) and muscle contraction. Acetylcholine remaining in the synaptic cleft is removed by hydrolysis catalyzed by the enzyme acetylcholinesterase (AChE), terminating the action potential and preventing overcontraction of the myocyte **(Fig. 1)**.

Myasthenia is fluctuating muscle weakness and fatigability on exercise due to a group of heterogeneous disorders of neuromuscular junction transmission. There are both congenital and acquired forms. The main etiologies are autoimmune and genetic.

ACQUIRED MYASTHENIC SYNDROMES

The classical clinical syndrome of disordered neuromuscular junction transmission is myasthenia gravis (MG), an acquired autoimmune antibody mediated postsynaptic disorder that is uncommon in childhood and may be seen in adolescents. MG has a prevalence of 5/100,000. It has a bimodal incidence being most common in women in their 2nd and 3rd decade of life and men in the 6th and 7th decade.

Pathogenesis
The disease is due to circulating antibodies to acetylcholine receptors (AChR), which bind to the receptor at the neuromuscular junction and prevent a normal action of acetylcholine in opening the calcium channel in the muscle fiber. About 80% of cases show antibodies to the AChR. A minority is positive for muscle specific kinase (MuSK) antibodies (10–12%). The disorder can be associated with thymic hyperplasia and tumors.

Clinical Features
Fatigable weakness may be generalized or confined to a specific group of muscles. Onset is insidious over weeks and months, often during the course of an intercurrent illness, and patients may show diurnal variation of fatigability and weakness. Periorbital muscles are often involved with ptosis that worsens during the day with diplopia in the evening. Weak facial, tongue and pharyngeal muscles can cause difficulty chewing, dysphagia and flaccid dysarthria. The disease may be confined to the eye muscles in younger patients. In older patients, bulbar symptoms are often associated. Weakness of limb movement tends to occur later in the disease and results in tiredness, fatigue on exertion and inability to sustain exercise. Deep tendon reflexes are normal. The course of the illness is variable. Symptoms may be more pronounced at times of emotional and physical stress. Diagnosis depends on demonstration of fatigable weakness in levator palpebrae superioris or limb muscles.

LAMBERT-EATON MYASTHENIC SYNDROME

This is a rare acquired neuromuscular junction transmission disorder first described in 1957. It can be further classified as cancer associated Lambert-Eaton myasthenic syndrome (Ca-LEMS), most often (>60%) seen as a paraneoplastic disorder with small cell carcinoma of the lung, though can be associated with other malignancies including non-Hodgkin lymphoma and leukemia, and non-cancer associated/autoimmune (NCa-LEMS). It is an autoimmune disorder with antibodies directed against presynaptic voltage-gated calcium channels in 85% patients. Onset is subacute with proximal muscles of lower limbs and shoulder most often affected. Involvement of cranial musculature is uncommon. Patients may improve transiently with exercise. Electromyography (EMG) study with tetanic stimulation shows facilitation in the size of the muscle action potential in contrast to decremental response seen in classical MG.

CONGENITAL MYASTHENIC SYNDROME

When symptoms and signs of myasthenia are of congenital or early childhood onset (< 2 years of age), it is defined a *congenital myasthenic syndrome (CMS)*. They may go unrecognized into adolescence and adulthood. It is often seen in a familial setting. The disease is rare with an incidence of less than 1 in 200,000 patients. CMS is a heterogeneous group of disorders, arising due to

1. Impulse arrives at the motor end plate causing release of Ach from vesicles in the axon terminus

Ca^{+2}

Ca^{+2} acts as an intermediate in causing exocytosis by Ach vesicles

2. ACH diffuses across the synapse to bind to receptors on the sarcolemma

ACH receptors (chemically regulated ion gates)

3. Binding of ACH to the receptors causes Na+ to enter the cell causing depolarization.

Polarized sarcolemma, produced by the sodium-potassium pump

4. If threshold depolarization occurs a new impulse (action potential) moves along the sarcolemma

5. Sarcolemma repolarizes:
   (a) K^+ leaves cell
   (b) Na/K pump restores polarity

6. ACH broken down by ACH-E (ACHase, cholinesterase).

Figure 1 Physiology of normal neuromuscular transmission

genetic mutations causing critical change in presynaptic, synaptic or postsynaptic proteins, leading to impaired neuromuscular junction transmission and rarely a chronic myopathy. The calcium dependent release of acetylcholine from the nerve terminals and the efficiency of released quanta generating a postsynaptic depolarization determine the efficiency of neuromuscular transmission. Symptoms persist throughout life and may respond to anticholinesterases.

Classification

A conceptual framework for understanding CMS is to classify them by site, as presynaptic, synaptic or postsynaptic and the molecular basis of the neuromuscular transmission defect **(Table 1)**. Genes responsible for the pathology at various levels are depicted in **Figure 2**.

Presynaptic syndromes The causative mechanisms involve the synthesis or packaging of acetylcholine quanta into synaptic vesicles. The most important and typical presynaptic defect is deficiency of choline acetyl transferase (ChAT), a rate limiting enzyme responsible for the synthesis of acetylcholine, resulting in decreased release of acetylcholine quanta. ChAT is found in high concentration in cholinergic nerve terminals and is encoded by the ChAT gene. Presynaptic defects are the least common of the CMS and account for about 6% of CMS.

Synaptic syndromes There is congenital deficiency of AChE localized on the end plate on the muscle surface. AChE breaks down acetylcholine and is found mainly at neuromuscular junction and brain cholinergic synapses. Its activity is to terminate synaptic transmission. It accounts for up to 15% of CMS.

Postsynaptic syndromes These are due to defects of the AChR (including the expression, aggregation or kinetic properties) and are the most common cause of CMS accounting for 70% of patients. Slow channel and fast channel syndromes also belong to this group. Reduced AChR expression can also be caused by defects of essential muscle intrinsic proteins *viz.* receptor-associated protein at the synapse (RAPSYN), MuSK and *DOK-7*. The latter has been identified as a cause of limb-girdle myasthenia.

Clinical Features

These children present with weakness of ocular, periorbital, facial, bulbar and respiratory muscles, worsened by exertion (crying, feeding and other activity). Babies can present with generalized floppiness. Weakness of extraocular and bulbar muscles results in ptosis, feeding difficulties, weak cry, and developmental milestones may be normal or delayed **(Fig. 3)**. Symptoms may progress during adolescence.

Symptoms can be episodic with severe weakness and respiratory insufficiency occurring during intercurrent illness with fever, excitement or without. Sudden critical weakness of bulbar and respiratory muscle weakness causing apnea and respiratory arrest is a critical symptom and hypoxic cardiac arrest can follow. CMS should be considered when infants and young children present with acute life-threatening events (ALTE) or

Table 1 Congenital myasthenia syndromes

Presynaptic defects (6%)
CMS with episodic apnea: Defect of choline acetyltransferase (ChAT)
Floppy and weak; extraocular, bulbar and respiratory muscles affected
Cardinal feature is episodic life-threatening apneas
Autosomal recessive (AR)

Synaptic defects (14%)
End-plate acetylcholinesterase (AChE) deficiency (AR)

Postsynaptic defects (70%)
Primary AChR deficiency with or without kinetic abnormality
Slow-channel syndrome AR
Fast-channel syndrome AR
Receptor-associated protein at the synapse (RAPSYN) deficiency
Sodium channel myasthenia

Defects in mechanisms of end-plate development and maintenance (10%)
DOK-7 myasthenia

Figure 2 Genes responsible for congenital myasthenia syndromes (as at 2014)
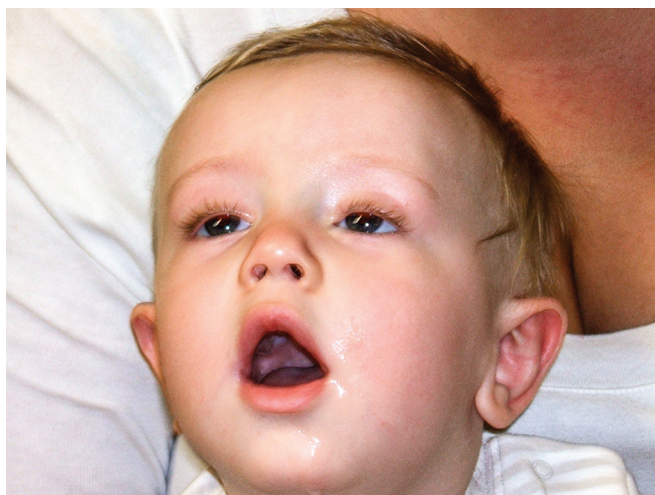
Figure 3 Infant with congenital myasthenia syndrome due to defect of Epsilon subunit of postsynaptic AChR. Note myopathic face with bilateral ptosis and open mouth

Figure 4 Tensilon (edrophonium test): A positive test is immediate elevation of both upper eyelids with resolution of ptosis after about a minute and lasting about 5 min

severe apneas. This is a particularly prominent feature of ChAT deficiency. Affected children may be well in-between episodes.

Neonatal myasthenia gravis Transport of AChR receptor subunit antibodies across the placenta can cause transient neonatal MG in up to 15% of infants born to mothers affected by autoimmune myasthenia. Ptosis, facial weakness, poor feeding, weak cry and respiratory insufficiency are present from birth. Cord blood sample should be taken at delivery to measure AChR receptor antibodies. Respiratory function and feeding must be carefully monitored in the infant. Symptoms and signs resolve by 3–4 weeks of age.

In older children and adolescents with myasthenic symptoms, both autoimmune myasthenia and CMS should be sought, initially with tests seeking antibodies against AChR or MuSK antibodies. During clinical examination, an important clue is muscle fatigue and weakness on sustained exertion that can be demonstrated by worsening ptosis during sustained upward gaze or measuring arm elevation or deep knee bends. Ocular muscle involvement may be absent or mild in some cases of AChE deficiency, the slow channel syndrome, receptor-associated protein of the synapse (*RAPSN)* deficiency or limb-girdle myasthenia caused by mutations in *DOK-7* or other genes. Deep tendon reflexes are often preserved though patients may be hyporeflexic.

INVESTIGATIONS IN SUSPECTED MYASTHENIA

Bedside Tests

Icepack test is an easily performed bedside test to seek support for the diagnosis of myasthenia. An icepack is held firmly over one eye (the test eye) for 2 min. Improvement in the ptosis, i.e., better elevation of the test upper eyelid relative to the opposite eye (control), suggests myasthenia as the cause of ptosis. This test relies on the fact that surface cooling of the muscle improves neuromuscular junction transmission.

Tensilon (edrophonium bromide) test shows rapid and transient resolution of symptoms and confirms myasthenia. Edrophonium is a short-acting anticholinesterase drug with rapid onset of action. This test should be done with placebo-control and ideally with an independent second observer and if possible video recording. There is a small risk of muscarinic side effects. Patient's heart rate and blood pressure have to be monitored with atropine being available (0.02 mg/kg/dose IV, maximum 2 mg). The test dose

of edrophonium 20 mcg/kg is given intravenously with a normal saline control. If there is no adverse effect within the 1st min, the rest of edrophonium 80 mcg/kg/dose (maximum total dose of 10 mg) is given. A positive test is immediate elevation of both upper eyelids with resolution of ptosis after about a minute and lasting about 5 min **(Fig. 4)**. A negative test does not exclude the diagnosis.

Serological Tests

Serum AChR antibodies are highly specific for MG and occur in 85% of those with generalized disease and 50% of those with ocular disease. Patient who are negative for AChR antibodies are referred to as *seronegative*. A subgroup of these patients are positive for MuSK antibodies. MuSK antibodies can be associated with MG in childhood (5–10%) and tend to be associated with a more refractory and severe disease course. Serological test for AChR antibodies and MuSK antibodies are negative in most patients with genetically determined CMS. The exception is neonatal onset MG, due to transplacental transfer of maternal AChR antibodies.

Myasthenia gravis is seen in association with autoimmune thyroid disease in 10% of patients. Thyroid function tests should be done in all patients. MG patients have increased incidence of familial autoimmune disease. HLAB8 and DR3 in young women and DR2 in older men are often associated.

Electromyography in Neuromuscular Disorders

In suspected neuromuscular junction disorders electrical activity of muscles (EMG) from a number of weak muscles may be recorded with surface electrodes, concentric needle electrodes and microelectrode needles in single fiber studies, the latter particularly for studies of neuromuscular transmission. The electrical activity recorded from normal muscles varies depending on the state of the muscles. Normal muscle is electrically silent when fully relaxed unless placed close to an end-plate region; following insertion or movement of a needle electrode, a short burst of activity lasting 2s or 3s may occur. Leading muscle activity motor unit potentials are recorded. The activity recorded from each single motor unit, i.e., a motor neuron and all the muscle fibers is the sum of the activity from those muscle fibers within the unit that are close to the needle. All motor unit potentials are usually bi- or triphasic with duration up to 15 ms and amplitude of up to 3 microvolts.

Any abnormality of diseased muscle during activity is best considered in terms of morphology of motor units and changes in recruitment pattern. The shape, amplitude and duration of motor unit potentials are determined by the compound activity of muscle fibers within that unit. In myopathic disorders, smaller amplitude shorter duration potentials are obtained due to loss of muscle fibers in the motor unit. In patients with MG or the myasthenic syndromes, minor abnormalities in EMG may be present. Motor unit potentials may be variable in amplitude and configuration and this change can be subtle. In MG, tetanic train (serial rapid)

Figure 5 Infant having needle EMG recorded from right orbicularis oculi with repetitive nerve stimulation (RNS) of facial nerve
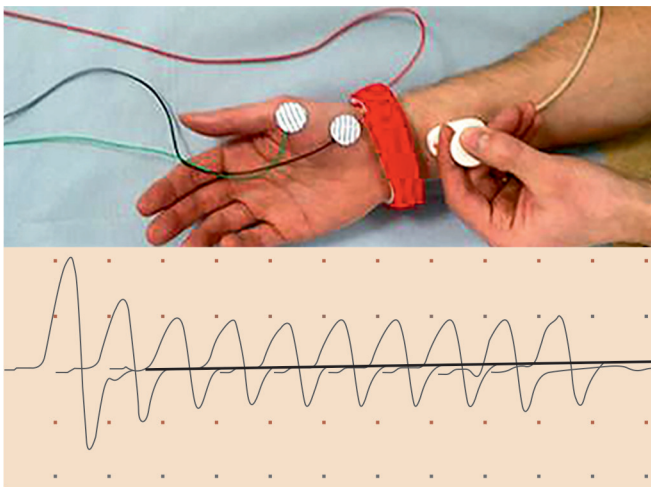
Figure 6 Surface EMG recorded from abductor pollicis brevis with tetanic train stimulation of median nerve at the wrist. Note reduction in compound muscle action potential (CMAP) amplitude from first and fourth responses

stimulation on EMG reveals progressive reduction in size of successive motor action potentials.

Confirmation of a clinical diagnosis of myasthenia needs recurrent nerve stimulation (RNS) of the motor nerve **(Fig. 5)** and recording of evoked CMAP. In children, this can be done relatively easily by stimulating the ulnar nerve and recording from the abductor digiti minimi, or the median nerve and recording from the abductor pollicis longus **(Fig. 6)**.

Short tetanic trains of 1–10 Hz, will not cause significant decrement in the size of evoked CMAP in normal individuals. EMG with repetitive nerve stimulation (RNS) shows decremental response of the CMAP amplitude at low frequency (2–3 HZ) in 65–80% patients. Its absence does not exclude the diagnosis.

Single fiber EMG (SFEMG) studies These are very helpful for detecting abnormalities of neuromuscular transmission. If a needle with one or more small recording electrodes along its length is inserted into muscle, it may be possible to position it so that recordings can be made from two or more single muscle fibers within a motor unit. When the muscle is contracted, individual fibers

will be activated with close temporal association. The activation of fibers should have a relatively fixed temporal relationship with little *jitter* (i.e., little variation in latency of activation of fibers) and no blocking (i.e., no absence of individual fiber activity). In disorders of neuromuscular transmission there is greatly increased jitter and evidence of neuromuscular block between the first and fourth or the first and fifth responses. Single fiber EMG studies look for failed or delayed conduction in pairs of muscle fibers supplied by a single nerve fiber. There is increased jitter or blocking. These findings occur in 90% cases of patients with generalized MG and smaller but significant proportion of CMS (60%).

Other Studies

The clinical and EMG phenotype of many genetically determined CMS is distinct. Targeted mutation screening for distinct and known clinical and EMG phenotypes, e.g. ChAT should be performed. Approximately 10% of patients with MG are found to have thymic tumors or hyperplasia, particularly older men, who should have chest CT/MRI with contrast.

TREATMENT OF ACQUIRED MYASTHENIC SYNDROMES

Myasthenia gravis responds to therapy with anticholinesterase drugs which slow the breakdown of acetylcholine at the neuromuscular junction. The usual agent used is pyridostigmine 30 mg to 60 mg 4 hourly in adults and 1–1.5 mg/kg/day in children under age 12 years. It has slower onset and longer duration of action with milder gastrointestinal effects than neostigmine. Atropine (0.6 mg twice daily) or probanthine is added to the regime to block unwanted muscarinic and autonomic effects of the anticholinesterases like colic and diarrhea.

Steroids reduce the effect of the disease and in patients with purely ocular myasthenia may be the most effective therapy. Steroids can be used in short courses with doses of 10 mg to 20 mg daily or on alternate days with maximum 2 mg/kg. Weaning from steroids should be slow with maintenance at the lowest possible dose.

In acute severe life-threatening myasthenia, plasmapheresis may give significant benefit; however, regular plasmapheresis does not appear to play a role in standard therapy of the disease.

If a thymic tumor or hyperplasia is detected, thymectomy is the treatment of choice although patients may take months to show benefit from the procedure. This is always indicated in patients with thymoma. Thymectomy also gives excellent results in patients who are AChR positive.

Infants with transient neonatal MG respond to anticholinesterase medication with resolution by 3–4 weeks of age. Steroid sparing agents such as azathioprine, methotrexate and mycophenolate are used in chronic MG. Rarely patients may need plasmapheresis or intravenous immunoglobulin infusions.

When MG patients on treatment deteriorate, it is important to determine if it is a cholinergic crisis due to excessive treatment or a myasthenic crisis due to inadequate and ineffective therapy. It is best to admit the patient, discontinue all therapy and observe the condition over a few days.

In LEMS, anticholinesterase medication is not helpful. Therapy with 3,4-diaminopyridine is beneficial. Plasmapheresis and intravenous immunoglobulin (IVIG) also have benefit.

TREATMENT OF CONGENITAL MYASTHENIC SYNDROMES

Except in a minority, anticholinesterase medications also benefit patients with CMSs. Pyridostigmine in doses of 1–1.5 mg/kg body

weight is usually used at a dosing frequency 3–4 hourly with fewer side effects. Prophylactic anticholinesterase therapy should be given to patients even if they are well between crises. Parents should be advised and warned about worsening of symptoms during intercurrent illness and fever with possible life-threatening respiratory arrests that may lead to hypoxic cardiac arrest. Parents must be trained in basic resuscitation and given bag and mask equipment for helping the child during a crisis during transport to hospital. In a minority of CMS cases, 3,4-diaminopyridine can be used in treatment.

Special precautions during anesthesia Particular care needs to be taken during any anesthetic procedure in all patients with myasthenia. Avoidance of neuromuscular blocking drugs is vital to ensure patient safety at this time. Certain drugs, such as aminoglycoside antibiotics (neomycin, streptomycin) and some tetracyclines and D-penicillamine, can worsen myasthenic weakness. The last mentioned drug may also independently produce a myasthenic syndrome.

PROGNOSIS

In a large number of patients with CMS, the disease becomes milder in their teens and adulthood.

MORE ON THIS TOPIC

Jayawant S, Parr J, Vincent A. Autoimmune myasthenia gravis. Handb Clin Neurol. 2013;113:1465-8.

Liew WK, Kang PB. Update on juvenile myasthenia gravis. Curr Opin Pediatr. 2013;25:694-700.

Pitt MC. Nerve conduction studies and needle EMG in very small children. Eur J Paediatr Neurol. 2012;16:285-91.

Punga AR, Ruegg MA. Signaling and aging at the neuromuscular synapse: lessons learnt from neuromuscular diseases. Curr Opin Pharmacol. 2012;12:340-6.

Schara U, Della Marina A, Abicht A. Congenital myasthenic syndromes: current diagnostic and therapeutic approaches. Neuropediatrics. 2012;43: 184-93.

IN A NUTSHELL

1. Myasthenia is fluctuating muscle weakness and fatigability on exercise due to a group of heterogeneous disorders of neuromuscular junction transmission. There are both congenital and acquired forms. The main etiologies are autoimmune and genetic.
2. Acquired myasthenia is due to circulating antibodies to AChRs, which bind to the receptor at the neuromuscular junction and prevent a normal action of acetylcholine in opening the calcium channel in the muscle fiber.
3. Congenital myasthenic syndrome(s) arise due to genetic mutations causing critical change in presynaptic, synaptic or postsynaptic proteins, leading to impaired neuromuscular junction transmission. The calcium dependent release of acetylcholine from the nerve terminals and the efficiency of released quanta generating a postsynaptic depolarization determine the efficiency of neuromuscular transmission. AChR and MuSK antibodies are absent.
4. Transport of AChR receptor subunit antibodies across the placenta can cause transient neonatal MG in up to 15% of infants born to mothers affected by autoimmune myasthenia.
5. Most patients with acquired or congenital myasthenia respond to therapy with anticholinesterase drugs.

Chapter 43.10
Hereditary Motor and Sensory Neuropathies

V Viswanathan

Hereditary motor and sensory neuropathy (HMSN) are a genetically heterogeneous group of disorders with variable ages of presentation. The typical patient has progressive distal weakness mild to moderate sensory loss, depressed or absent tendon reflexes and high arched feet. Four major categories of HMSN have been described although each of these are further categorized based on molecular and linkage analysis. The terms Charcot-Marie-Tooth (CMT) disease and hereditary sensory and motor neuropathy are interchangeable. The exact prevalence of the disorder is unknown although it is said to occur in 36 in 100,000 persons.

The genetic defect results in structural/functional deficiencies in axons or myelin sheath of the nerves and that causes the clinical features that we see. The primary demyelinating neuropathies are CMT1, CMT3 and CMT4 and primary axonal neuropathies CMT2. However, the classification of these varieties is not that rigid and many times the pathologies are intermingled due to the close interaction between the Schwann cells and the neurons.

The disease is named after the people who classically described it: Jean-Martin Charcot (1825–1893) and his pupil Pierre Marie (1853–1940) and Howard Henry Tooth (1856–1925) (*Peroneal type of progressive muscular atrophy, dissertation*, London, 1886).

CLASSIFICATION

The initial classification of these disorders was done by Dyck and Lambert in 1968 as HMSNs, the hereditary sensory and autonomic neuropathies and the hereditary motor neuropathies. Harding and Thomas further subdivided the HMSN in a group with motor nerve conduction velocity (mNCV) below 38 m/s (HMSN-type 1) and a group with mNCV above 38 m/s (HMSN-type II). The present classification takes into account the clinical, electrophysiological, pathological and genetic criteria for the classification **(Table 1)**. As molecular genetics becomes more advanced over the recent years there are over 50 chromosomal loci described for HMSN and 33 genes with mutations causing HMSN including 24 phenotypic forms of dominant motor and sensory neuropathy. Mutations in

Table 1 Current classification of Charcot-Marie-Tooth disease and related neuropathies

Neuropathic type	Key neuropathic features
CMT 1	Dominantly inherited with low NCV
CMT 2	Dominantly inherited with normal or low normal NCV
CMT X	X-linked inherited
HNPP	Dominantly inherited with focal nerve lesions
Dejerine Sottas syndrome	Variable inheritance with extremely low NCV and severe disability
Congenital hypomyelination	Sporadic inheritance with extremely low NCV and extremely severe disability
CMT 4	Recessively inherited CMT

Abbreviations: CMT, Charcot-Marie-Tooth; NCV, nerve conduction velocities; HNPP, hereditary neuropathy with liability to pressure palsies.

four genes (*PMP22, GJB1, MPZ* and *MFN2*) cause more than 90% of the genetically identifiable cases of CMT in North America.

There are rare types of HMSN described with associated corpus callosal agenesis suggesting that sometimes you can get gene defects causing structural and neuro-degenerative problems in the same child with early onset of developmental issues.

CLINICAL FEATURES

The age of onset is within the first or second decade of life although it has been reported to be as late as seventh decade. The children present typically with slowly progressive difficulty with walking/running and frequent tripping/falls. The gait is usually a high stepping gait due to the weakness and wasting is seen in the distal muscles of the legs. Most patients develop high arched feet and clawing of the toes with thinning of the calf muscles noticed by the parents **(Fig. 1)**. The disease later progresses to involve the hands and forearms resulting in difficulties with writing and manipulating small objects **(Fig. 2)**.

In all cases, distal usually symmetrical sensory deficits-stocking or glove distribution are present but very often not noticed by the child/family. The weakness and atrophy is predominant in the peroneal group of muscles in the legs and the small muscles of the hand and feet. The tendon reflexes are diminished or absent especially in the ankle. Wasting of the foot and distal lower extremity muscles develop over time and may produce the classical *inverted champagne bottle* appearance. In the demyelinating forms of HMSN, nerve hypertrophy may be visible and thickened nerves such as the greater auricular nerve may be palpable. The course of the disease is often insidious and most patients do not or only late in life become wheelchair dependent.

Charcot-Marie-Tooth Disease 1

This is an autosomal dominant form of demyelinating neuropathy and accounts for about 50% of all cases. There are four different variants described depending on the genetic abnormality and the subtypes are clinically indistinguishable. Family history is usually present. Although the clinical features may start in childhood with pes cavus, weakness of peroneal group of muscles and diminished tendon jerks, this does not cause severe disability in childhood. Eventually after the age of 20 years, the weakness spreads to the proximal muscles of the legs and hands. Scoliosis is unusual. Cramps with exercise may occur. Position sense

Figure 1 Pes cavus foot deformity

Figure 2 Claw hand deformity

becomes impaired in the fingers and toes. Hip dysplasia may be an associated feature.

Charcot-Marie-Tooth Disease 2

The clinical phenotype is similar to CMT 1 except that the nerve conduction velocity (NCV) in this condition is normal or near normal. This also has an autosomal dominant inheritance pattern. There are seven different subtypes described depending on the chromosomal locus. These patients have less sensory loss as compared to CMT 1. The progression of symptoms is typically slow and disability does not occur until middle adult life. Prominent vocal cord and respiratory paralysis (intercostals and diaphragmatic) occurs in CMT 2C. In CMT 2D prominent weakness and atrophy of the hands has been reported.

Charcot-Marie-Tooth Disease 3

Dejerine Sottas Disease

This is a severe type of demyelinating neuropathy of infancy and childhood associated with slow NCV, elevated cerebrospinal fluid protein, marked clinical weakness and hypertrophic nerves with onion bulb formation.

Charcot-Marie-Tooth Disease 4

The inheritance pattern for this group is autosomal recessive. Based on the genetic locus and the protein that is deficient, this has been further subdivided into seven different types. The clinical features of distal muscle weakness start by around the second year of life and progress to involve the proximal muscles by about 10 years of age. They may have associated mild sensory loss, absent deep tendon reflexes and skeletal deformities. Scoliosis appears as age advances. The nerve conduction studies in these children show severe demyelinating type of neuropathy with marked reduction in the NCV to around 15–17 m/s.

Charcot-Marie-Tooth Disease X (CMTX)

This is an X-linked dominant condition. The mutations are specifically in the connexion 32 gene. The males are affected primarily while the females are only mildly affected or asymptomatic. The clinical features are very similar to CMT 1A although more severe. The symptoms develop during the first decade and then slowly progress over a period of time. The initial clinical features are very similar to the other types with foot drop and absent tendon reflexes with mild to moderate sensory loss in the feet. Hearing loss has been described with this condition.

NEUROPHYSIOLOGY

Marked slowing of NCV is the hallmark of CMT 1. Harding and Thomas found that median motor NCV of 38 m/s was a useful value in separating the demyelinating variety of CMT 1 and the axonal CMT 2. The conduction slowing was evident in children with CMT 1 by the age of 2 years and appeared to progressively drop over time, stabilizing by about 5 years of age. A reduction in the compound muscle action potential was also an early finding, present in recording from the foot in 50% of the children by the age of 5 in CMT 1. Weakness does not appear to correlate with the NCV. Conduction velocity changes very little over many years despite progressive neurologic disability.

MANAGEMENT

The management is mainly supportive. No specific treatment is available. Early in the course of the disease regular strengthening exercises for the feet and legs with active stretching of the feet may be beneficial. The most important aspect of care is the care for the feet and prevention of early deformities. Regular/gentle stretching at the ankles/feet may be of considerable benefit in helping the maintain gait and prevent early onset of foot drop. Use of well made, light weight, ankle foot orthosis (AFO) with good lining of cushion/padding to prevent rubbing/ulceration in the feet is important. These can be made in such a way that it slips into the shoes so that the child is able to walk and take care of his day-to-day activities comfortably. The AFOs need to be periodically checked and adjusted/a new one made as the children grow and many times they become too small/too tight and uncomfortable for the children to wear them. Do remember that these children also have some sensory loss in the feet and so they are liable for trophic ulcers in the feet and these need to be looked for when you examine them periodically.

We should also monitor for scoliosis every time they visit for follow-up and look at posture/positioning in the chair/wheel-chair and give appropriate advice. It is also important to help with some exercises for the hands, in particular for the small muscles of the hands and to help them to continue writing at school for as long as possible. Now with the support system being offered for education for these children, many of them may be provided suggestions/advice regarding provision of extra time to write examinations, overlooking the poor hand writing and the use of scribes for the exams if necessary. Use of other aids like computers may be looked at although this may be equally as difficult for these children. One of the other common issues that these children face is abnormal weight gain as soon as they have marked difficulties with ambulation and so appropriate advice regarding the diet from a dietician would be important.

It is hoped that as the genes causing the various forms of HMSN are identified, more specific therapies may become available. Clinical trials using high dose vitamin C have not shown any clinical benefit in adults and children with HMSN type 1A, despite promising effects in transgenic mouse model.

GENETIC COUNSELING AND PRENATAL DIAGNOSIS

With the advent of molecular testing and the availability of the same commercially more and more children can be diagnosed precisely and the genetic mutations identified. This enables us to not only counsel the family about the chance of recurrence in the next pregnancy but also to perform prenatal diagnosis and even help prevent the recurrence of the same disease in the family.

Nowadays with the genetic tests and good neurophysiology facilities being available the need for nerve biopsy as a diagnostic tool is very limited.

IN A NUTSHELL

1. Hereditary motor and sensory neuropathy is a genetic disorder involving the motor and sensory nerves.
2. May be as a result of demyelination or axonal involvement.
3. The clinical varieties are similar mainly involving the legs and the hands.
4. There is marked genetic heterogeneity.
5. Age of onset varies with some starting in childhood and others in adult life.
6. Diagnosis is mainly by the clinical presentation, neurophysiology and genetic studies.
7. There is no definitive therapy as such.
8. Supportive care includes appropriate stretching exercises and splints.
9. Periodic follow-up of these children is needed to observe for scoliosis/trophic ulcers.
10. Genetic counseling and provision of prenatal diagnosis will help prevention of recurrence.

MORE ON THIS TOPIC

Barisic N, Claeys KG, Sirotkovic-Skerlev M, et al. Charcot-Marie-Tooth Disease: a clinico-genetic confrontation. Ann Hum Genet. 2008;72:416-41.

Benstead TJ, Grant IA. Progress in clinical neuroscience: Charcot-Marie-Tooth disease and related inherited peripheral neuropathies. Can J Neurol Sci. 2001;28:199-214.

Bird TD. Charcot-Marie-Tooth hereditary neuropathy overview. In: Genetests: Medical Genetic Knowledge base. University of Washington, Seattle. From: http://www.genetests.org. Accessed on May 4, 2014.

Dyck PJ, Chance P, Lebo R, Carney JA. Hereditary motor and sensory neuropathy. In: Dyck PJ, Thomas PK. Peripheral Neuropathy. 3rd ed. Philadelphia: WB Saunders; 1993. pp. 1094-136.

Fenichel GM. Clinical Paediatric Neurology: a Sign and Symptom Approach. 5th ed. New Delhi: Saunders; 2005.

Kaku DA, Parry GJ, Malamut R, et al. Nerve conduction studies in Charcot-Marie-Tooth polyneuropathy associated with a segmental duplication of chromosome 17. Neurology. 1993;43:1806-8.

Krajewski KM, Lewis RA, Fuerst DR, et al. Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A. Brain. 2000;123: 1516-27.

Nicholson GA. The dominantly inherited motor and sensory neuropathies: clinical and molecular advances. Muscle Nerve. 2006;33:589-97.

Saporta MA, Shy ME. Inherited peripheral neuropathies. Neurol Clin. 2013;31: 597-619.

Chapter 43.11
Autonomic Neuropathies
Rachana Dubey, Ashok Jaryal, Sheffali Gulati

JN Langley first proposed the term autonomic nervous system (ANS) in 1921 and described its subdivisions as sympathetic, parasympathetic and enteric nervous system. ANS is ubiquitous and orchestrates important functions in many systems in the human body. The symptoms of ANS disorders are thus widespread and confounding due to multisystem involvement. Etiology of autonomic disorders is diverse; Familial dysautonomia was first described genetic autonomic disorder with many additions in primary category at present and ever expanding list of secondary involvement of ANS. Limited availability of diagnostic tests, lack of normative data in pediatric population and few treatment options are obstacles in managing pediatric autonomic disorders optimally.

THE ANATOMY AND PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

The ANS involves all major organs and consists of involuntary motor/effector system that is divided into sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions, each with a central and a peripheral component. In addition, there is an important enteric division. Outflow can occur independently or it is regulated and integrated by the central autonomic network (CAN). Embryonic development of the ANS is closely related to the development of the sensory nervous system; both have their embryonic origins in the multipotential neural crest cells. These cells migrate and develop into sensory and autonomic ganglia as well as the adrenal chromaffin cells.

Stimulation of *sympathetic system* leads to stimulation of many receptor systems resulting in dilation of the pupil, increase in glandular secretions, bronchodilation, increase in heart rate, decrease in gastrointestinal tract motility, and utilization of energy substrates. The *parasympathetic system* tends to have more local responses, but some effects may be multisystem, particularly with the wide-ranging innervation of the vagus nerve. **Table 1** suggests that they may not be exactly antagonistic contrary to popular belief.

Table 1 Effects of sympathetic and parasympathetic stimulation on various organs

Organ	Sympathetic nervous system	Parasympathetic nervous system
Heart	Increased rate Positive inotropism	Decreased rate Negative inotropism
Blood vessels (arterioles)	Constriction	None
Lungs	Bronchodilation	Bronchodilation
Gastrointestinal	Decreased motility	Increased motility
Kidney	Decreased output	None
Urinary bladder	Relax detrusor Contract sphincter	Contract detrusor Relax sphincter
Lacrimal glands	Slight secretion	Secretion
Salivary glands	Slight secretion	Secretion
Sweat glands	Secretion	Palmar sweating
Eyes		
Pupils	Dilatation	Constriction
Ciliary muscles	Relax (far vision)	Constrict (near vision)

SYMPTOMS OF AUTONOMIC DYSFUNCTION

Because the ANS and its CAN component have extensive effects that involve multiple systems, clinical manifestations can be extremely varied. When more than one system is affected, then a more global autonomic disorder should be considered on the basis of age at presentation. To understand these symptoms, a system wise approach is more helpful **(Table 2)**.

AUTONOMIC FUNCTION TESTS

There is growing need for objective quantitative autonomic function test centers for children and simultaneously to generate normative data in pediatric population. Laboratory testing has been developed to evaluate the functioning of cardiovagal, adrenergic and sudomotor aspects of the ANS **(Table 3)**.

Heart Rate Response to Deep Breathing (HRDB)

The HRDB provides an objective measure of the normal physiological response to breathing (sinus arrhythmia) **(Fig. 1)**. With a combination of verbal coaching and visual pacing, subjects are asked to breathe slowly and deeply at 5–6 times/minute. Heart rate during 8 cycles (inspiration and expiration each taking 5 seconds) is recorded and HRDB is calculated as the mean of the consecutive differences between maximal and minimal heart rate. Normative values exist for ages more than 9 years and HRDB is inversely related to age.

Heart Rate Variability

Heart rate variability (HRV) is measured by monitoring electrocardiogram for variable intervals (5 minutes to 24 hours) and analyzing R-R intervals. HRV can be reported as time domain or frequency parameters. HRV is an objective measure of the neural influences upon heart rate, which are due to naturally

Table 2 System-wise symptoms of autonomic nervous system dysregulation

System	Sign/dysfunction	Symptom
Cardiovascular system	Hypertension	Headache, visual symptoms
	Hypotension	Dizziness, light-headedness, blurring of vision, presyncope or syncope
	Arrhythmias	Palpitations, presyncope or syncope, acute life-threatening events
	Vasomotor changes	Mottling, peripheral cyanosis, blotching
Respiratory system	Alveolar hypoventilation	Apnea/cyanosis in sleep
	Apnea (insensitivity to hypoxia and hypercarbia)	Breath holding spells, acute life-threatening events, syncope
Sudomotor	Sweating disturbances	Hypohidrosis or hyperhidrosis, dry skin, clammy hands and feet, hyperthermia
Gastrointestinal	Oropharyngeal and esophageal dysmotility	Feeding difficulties, salivation, recurrent aspiration pneumonia
	Gastroesophageal reflux	Nausea, recurrent vomiting, aspiration pneumonia
	Colon dysmotility	Constipation, diarrhea, abdominal distension

Table 3 Autonomic function tests

Organ system	Autonomic component	Autonomic test
Cardiovascular system	Cardiovagal	1. Heart rate response to deep breathing (HRDB) 2. Heart rate response to standing (HRST) 3. Heart rate response to squatting (HRSQ) 4. Valsalva ratio (VR) 5. Heart rate variability (HRV)
	Adrenergic	1. Valsalva maneuver 2. Head-up tilt test (HUT) or tilt table test 3. Sympathetic skin response (SSR) 4. Biochemical (catecholamine levels)
Respiratory system	Control of breathing during awake and sleep states	Apnea monitoring Exogenous ventilator challenges Polysomnography Awake and asleep physiologic testing
Skin	Sudomotor	Quantitative sudomotor axon reflex test (QSART or QSWEAT) Thermoregulatory sweat test (TST)
Pupillary muscles	Sympathetic and parasympathetic	Pupillometry
Gastrointestinal system	Gastrointestinal motility	Gastric scintigraphy Colonic transit

opposing sympathetic and parasympathetic signals. HRV values should be interpreted according to physiological state. It can also be evaluated through visualization of scatter plots of successive R-R intervals known as Poincaré plots **(Figs 2A and B)**. Narrow scatter pattern will suggest decreased HRV and characteristic patterns are helpful in recognizing diseases like congenital central hypoventilation syndrome (CCHS) and rapid onset obesity with hypothalamic and autonomic dysfunction (AD).

Head-up Tilt or Tilt-table Test

Head-up tilt has been widely used for the evaluation of orthostatic tolerance. Lower extremities are restrained with the feet placed on a footboard so that no muscle is used to maintain the upright posture. In HUT, the patient is initially at rest supine for 10–30 minutes, then passively head end is elevated to 60–80°. In this state heart rate, blood pressure, and clinical status are monitored for 10–30 minutes. Patients might experience presyncope or syncope and test is aborted in this situation. Patients with orthostatic hypotension may **(Fig. 3)** or may not **(Fig. 4)** show compensatory increment in the heart rate in tilt position depending upon the functional state of baroreflex.

Sudomotor Testing (Quantitative Sudomotor Axon Reflex Test [QSART] or Quantitative Sweat Measurement System [QSWEAT])

These tests provide information about sweat glands and postganglionic sympathetic nerve fibers functions. QSWEAT is commercially available kit which is based on QSART. In QSWEAT, surface disks are placed through which a low-intensity current is passed to iontophorese acetylcholine through the skin and stimulate sudomotor sympathetic axons resulting in sweat production. The same capsule is used to provide acetylcholine for iontophoresis, guide the constant-current stimulus and collect data regarding the volume of local sweat formation. Sweat production is expressed in mL/cm^2 and compared to normative data.

Heart rate response to deep breathing (HRDB)
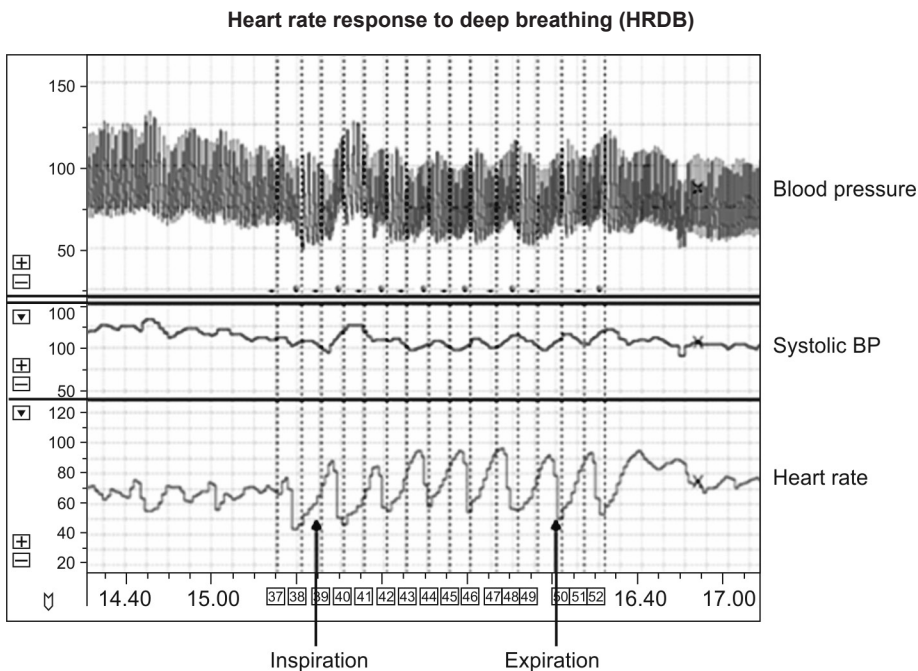
Figure 1 This record shows changes in the blood pressure and heart rate during deep breathing test or alternate deep inspiration and expiration. The blood pressure was measured noninvasively by Finometer®midi (Finapres Medical Systems, USA). The systolic pressure was computed from the pressure wave form while the beat-to-beat heart rate was derived from lead II of ECG

Heart rate variability in from of Poincare plots

A. Normal

B. Diabetic outonomic neuropathy
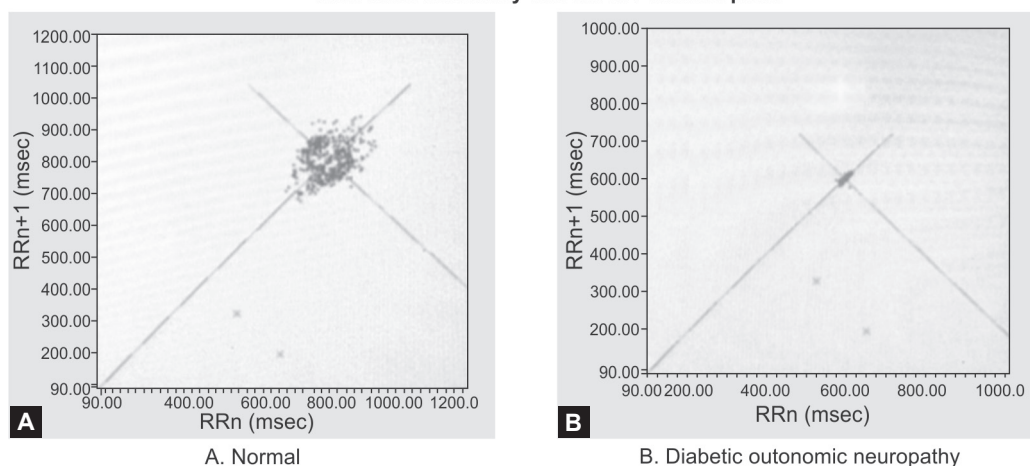
Figures 2A and B Poincare plots of healthy control. (A) Typical distribution of RRn and RR(n+1) in both axes. In loss of autonomic control of the heart, the distribution of the events is lost leading to centralization of the points; (B) The Poincare plot was made by HRVSoft (version 1.1, Autonomic Function Test Laboratory, AIIMS, New Delhi, India)

Head-up tilt (70°) in a patient of orthostatic hypotension without symptoms
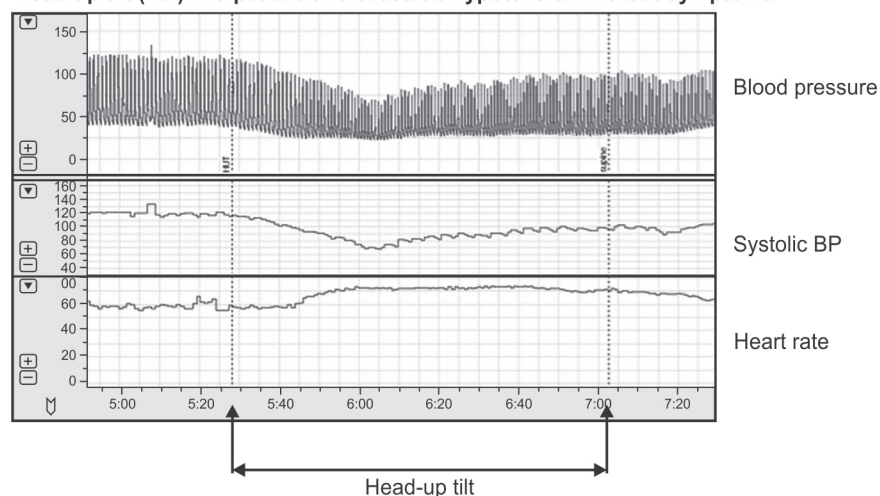
Figure 3 This record shows changes in the systolic blood pressure and heart rate with passive head-up tilt (for 15 seconds) in a patient of orthostatic hypotension without symptoms. Note the progressive decrease in the blood pressure with concomitant increase in the heart rate. The blood pressure was measured noninvasively by Finometer®midi (Finapres Medical Systems, USA). The systolic pressure was computed from the pressure wave form while the beat-to-beat heart rate was derived from lead II of ECG

SYNCOPE IN CHILDREN AND ADOLESCENTS

Syncope is defined as the abrupt loss of consciousness and postural tone resulting from transient global cerebral hypoperfusion followed by spontaneous complete recovery. *Presyncope* is the feeling that one is about to pass out but remains conscious with a transient loss of postural tone. In the young patient, syncope may result from a fall in systolic pressure below 70 mm Hg or a mean arterial pressure of 30–40 mm Hg.

The syncopal event is typically preceded by a *prodrome* lasting from few seconds to 1–2 minutes with symptoms such as nausea, epigastric discomfort, blurred or tunnel vision, muffled hearing, dizziness, light-headedness, palpitations, pallor, cold and clammy skin, or weakness. These symptoms may occur variably in patients. Pediatric syncope is in general benign disorder but careful evaluation should be done to exclude a life-threatening cardiac or noncardiac disorder. There are many differential diagnoses to syncope in children and adolescents **(Box 1)**.

BOX 1 Differential diagnosis of syncope in children

- Neurocardiogenic syncope (vasodepressor or vasovagal)
- Orthostatic hypotension (OH)
- Postural orthostatic tachycardia syndrome (POTS)
- Cardiovascular mediated syncope
- Convulsive syncope
- Psychogenic syncope/panic attacks
- Situational syncope: Coughing, sneezing, micturition, defecation, deglutition (cold liquids), trumpet playing, suffocation, weight lifting, diving, etc.
- Drug and toxin induced
- Metabolic: Hypoglycemia, electrolyte imbalance, endocrine disorder.

Epidemiology

Syncope affects 15–25% of the children and adolescents. The incidence peaks around the ages of 15–19 years and there appears to be a female predominance. Before age 6, syncope is uncommon

Head-up tilt (70°) in a patient of orthostatic hypotension
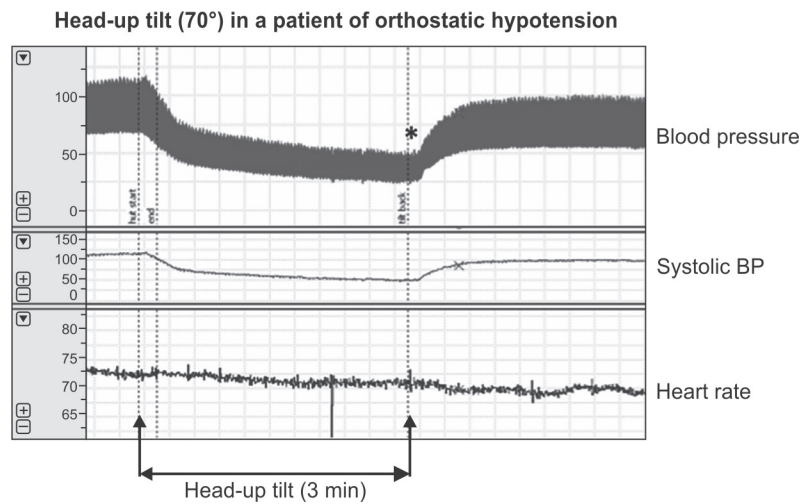
Figure 4 This record shows a changes in the systolic blood pressure and heart rate with passive head-up tilt (over 15 seconds) in a patient of orthostatic hypotension who developed symptom (*) during the test leading to termination of test. Note the progressive decrease in the blood pressure without concomitant increase in the heart rate. The blood pressure was measured noninvasively by Finometer®midi (Finapres Medical Systems, USA). The systolic pressure was computed from the pressure wave form while the beat-to-beat heart rate was derived from lead II of ECG

and is seen in association with seizures, breath-holding spells, and cardiac arrhythmias. In children, neurocardiogenic syncope or vasovagal syncope or vasodepressor syncope is the most frequent cause of syncope (60–80%). The 5-year recurrence rate of syncope ranges from 33% to 50%.

Etiology

Detailed history of the event and physical examination will help in categorizing syncope into the three major types: (1) Neurocardiogenic syncope (neurally mediated/vasovagal/vasodepressor); (2) Cardiovascular-mediated syncope; and (3) Noncardiovascular syncope.

Neurocardiogenic Syncope

Previously known as vasodepressor, vasovagal, or neurally mediated syncope, is the most common cause of syncope. The history includes usual triggers such as postural changes, prolonged standing or sitting, obnoxious stimuli (anger, pain, sight of blood), and a positive family history.

Cardiovascular-mediated Syncope

In children, cardiovascular-mediated syncope is less frequent than in adults. It has a higher mortality and incidence of sudden death than neurally mediated syncope. A detailed cardiac history and important *red flags* **(Box 2)** suggest a need for an urgent pediatric cardiology referral. Many cardiac disorders can present as cardiovascular syncope in children **(Box 3)**.

BOX 2 Cardiac red flags in history of syncope

- History of heart murmur or congenital heart disease
- Acute attacks associated with hyperpnea or cyanosis
- Syncope during exercise or with exertion
- Family history of early sudden cardiac death, long QT syndrome, sensorineural hearing loss, familial heart disease
- Medications that can cause long QT syndrome, arrhythmias
- Absence of usual premonitory symptoms or precipitating factors associated with neutrally mediated syncope
- Unusual syncope triggers such as loud noises, fright, or extreme emotional stress.

BOX 3 Cardiovascular causes of syncope in children

- Arrhythmias
  - Complete heart block
  - Sick sinus syndrome
  - Tachyarrhythmias:
    - Supraventricular (Wolff-Parkinson-White-syndrome)
    - Ventricular
  - Ion channel abnormalities
    - Long QT syndrome (congenital or drug induced)
    - Brugada syndrome
- Cardiac: Structural
  - Aortic stenosis (valvular)
  - Hypertrophic obstructive cardiomyopathy
  - Coronary artery anomalies
  - Primary pulmonary hypertension
  - Eisenmenger syndrome
  - Mitral valve prolapse
  - Neuromuscular disorders
- Cardiac tumors.

Diagnostic Evaluation

A detailed history, a comprehensive clinical examination and an ECG have a combined diagnostic yield of 50% **(Box 4)**. The event history is most important in making diagnosis of syncope. Diagnostic evaluation should include an ECG on all patients with syncope, especially if it occurs with exercise and in younger children. All patients with risk factors for cardiac disease should be evaluated further by performing echocardiography, Holter or event monitor. Electroencephalography and neuroimaging are not recommended unless the loss of consciousness is not suggestive of syncope or seizure-associated syncope is suspected.

Management

The objective of treatment for neurocardiogenic syncope is to prevent recurrences; which leads to impaired quality of life, psychological distress, and substantial morbidity including school absenteeism. The mainstay of treatment of neurocardiogenic syncope is education and counseling of the patient, parents and teachers.

- Hematological and biochemical:
  – Complete blood count (CBC)
  – Serum iron, serum ferritin
- Cardiac evaluation:
  – Electrocardiogram (ECG)
  – Echocardiography
  – Holter or event monitor
- Autonomic evaluation:
  – Neurocardio autonomic reflex testing with and without tilt table testing
  – Quantitative sudomotor axon reflex test (QSART)
  – Thermoregulatory sweat test (TST)
- Miscellaneous:
  – Urine specific gravity and urinary sodium levels
  – Pregnancy test in menstruating adolescents.

Table 4 Primary and secondary disorders of pediatric autonomic nervous system dysregulation

Category		Disorders and Conditions
Primary	Developmental, genetic and syndromic	• Congenital central hypoventilation syndrome (CCHS) • Hereditary sensory and autonomic neuropathies II / III /IV • Alacrima, anhidrosis, adrenal insufficiency (AAAS)/Allgrove syndrome • Rett syndrome • Fragile X syndrome • Prader-Willi syndrome • Sodium channelopathies (*SCN9A* gene)
	Metabolic	• Mitochondrial disorders • Porphyria • Fabry disease • Menkes' disease • Dopamine β-hydroxylase deficiency and other neurotransmitter disorders (Norepinephrine transporter defect)
Secondary	Autoimmune	• Guillain-Barré syndrome • Paraneoplastic autoimmune polyneuropathy • Autoimmune neuropathy or ganglionopathy • Postural orthostatic tachycardia syndrome (POTS) • Lambert-Eaton syndrome or myasthenia gravis
	Paroxysmal disorders	• Recurrent syncope • Pheochromocytoma • Postural orthostatic tachycardia syndrome • Abdominal migraine and cyclic vomiting
	Disorders with associated autonomic dysregulation with known and unknown etiologies	• Diabetes mellitus and other endocrine disorders (thyroid disorder, Addison's disease, etc.) • Autism spectrum disorder • Migraine • Epilepsy • Illnesses causing small fiber neuropathies • Rapid onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysfunction (ROHHAD) • Drugs
	Infections	• HIV • Leprosy • Diphtheria • Chagas' disease • Botulism

Nonpharmacological Measures

The benign nature of these events should be explained and reassurance that these episodes would not result in epilepsy or sudden death. These will resolve within months to about 5 years after onset. Patients should be encouraged to maintain adequate hydration (1.5–2.5 L of water/day) and enhance dietary salt (2–5 g/day) intake. Patients should learn to recognize and avoid triggers. If the patients are on hypotensive medication, then they should be modified or discontinued. Isometric counterpressure maneuvers: leg crossing, buttock tensing and squatting may help in appropriate situations.

Drug Therapy

If despite conservative measures the syncopal episodes are recurrent, pharmacologic therapy may be tried. A wide variety of pharmacologic agents are given for prevention of neurocardiogenic syncope in children and adolescents.

- β-*adrenergic antagonists*: Propranolol (0.5–4 mg/kg/day), Atenolol (1–2 mg/kg/day)
- α-*adrenergic receptor agonist*: Midodrine (2.5–10 mg tid), pseudoephedrine (60 mg bid)
- *Mineralocorticoids*: Fludrocortisone (0.1–0.3 mg/day)
- *Others*: Anticholinergics, selective serotonin receptor reuptake inhibitors.

None of these agents, however has shown a consistent therapeutic benefit. Low-dose midodrine is currently recommended as first-line therapy for refractory neurocardiogenic syncope in children. Fludrocortisone should be used with increased salt intake for optimal effect.

AUTONOMIC DISORDERS

Table 4 lists the primary and secondary autonomic disorders.

HEREDITARY/PRIMARY AUTONOMIC DISORDERS

Hereditary Sensory and Autonomic Neuropathies

The hereditary sensory and autonomic neuropathies (HSANs) are due to genetic mutations that affect migration, differentiation, and survival of specific neurons, so that to some extent they can be considered neurocristopathies. With the exception of HSAN I, which is autosomal dominant disorder and starts in second decade, the other HSANs are present at birth and predominantly transmitted as autosomal-recessive disorders. In all HSAN patients, intradermal injection of histamine phosphate fails to elicit a normal axon flare response, which suggests reduced pain fibers as flare response depends on continuity of the peripheral axon and its cell body in the dorsal root ganglion. AD is associated with II, III, and IV subtypes of HSAN **(Table 5)**.

Hereditary Sensory and Autonomic Neuropathies-II

Classification of the HSANs is an ongoing process and has been aided by attempts to categorize the phenotype and identify the disease causing mutations; thus there are subtypes of HSAN I

Table 5 Classification of hereditary sensory and autonomic neuropathies

HSAN type	Chromosome/ Gene	Age at onset	Inheritance	Autonomic involvement
HSAN-I				
Type IA	9q22-q22.3/ SPTLC1	After second decade (all subtypes)	Autosomal dominant (all ubtypes)	Absent (all subtypes)
Type IB	3p24-p22/ Unknown			
Type IC	3q21/RAB7			
Type ID	Unknown/ Unknown			
HSAN-II				
Type IIA	12p13.33/HSN2 or WNK1	Birth-first decade	Autosomal Recessive	Present
Type IIB	5p15.1/ FAM134B	Childhood	Autosomal Recessive	Present
Type IIC	2q37.3/KIF1A	Childhood	Autosomal Recessive	Present
HSAN-III	9q31-33/ IKBKAP	Birth	Autosomal Recessive	Present
HSAN-IV	1q21-22/NTRK1	Birth	Autosomal Recessive	Present
HSAN-V	1p13.1/NGFB	Childhood	Autosomal Recessive	Absent

and II. Patients within the HSAN II classification exhibit profound sensory loss involving large and small fiber modalities. HSAN II is also known as Morvan's disease.

Clinical Features
Pain, temperature, and to a varying degree, position sense, are involved, and unrecognized injuries and fractures, as well as Charcot joints are seen frequently. Self-mutilation often begins with eruption of primary dentition and results in lip and tongue injuries. Deep tendon reflexes are depressed. Sensory nerve action potentials are absent. Taste sensation, corneal and gag reflexes are diminished. Hypotonia is common and may contribute to scoliosis. Cognition and motor functions are usually normal. AD varies from minimal to complex. Severe neonatal involvement is characterized by feeding problems and frequent apnea.

Management
Gastroesophageal reflux is common and sweating function is variable as hyperhidrosis as well as areas of anhidrosis can occur in the same patient. Blood pressure liability is not a feature of HSAN-II. Treatment is mainly symptomatic and preventative.

HSAN-III (Familial Dysautonomia, Riley Day Syndrome)
Familial dysautonomia was first genetic autonomic disorder to be recognized and is rarely seen outside Ashkenazi Jewish population. FD mutations lead to tissue-specific reductions in normal IKAP or hELP1 protein with subsequent downregulation of genes involved in neurogenic differentiation and migration of neural crest cells; finally affecting development of sensory and autonomic neurons. Unmyelinated and small myelinated neurons in the peripheral sensory nervous system and the ANS are reduced in number.

Clinical Features
- *Sensory symptoms* are less pronounced in FD compared to other HSANs. Corneal reflexes are depressed and gustatory sensation is diminished, because of absence of lingual fungiform papillae.
- *Motor symptoms* Absence of functional muscle spindles explains the loss of deep tendon reflexes and impaired sensorimotor control during walking, resulting in an ataxic gait. Motor milestones are commonly delayed, but cognition is usually normal.
- The *autonomic disturbances* are extensive. These patients have absence of tears (alacrima) with emotional crying and feeding difficulties due to poor oral coordination and hypotonia. Gastroesophageal reflux and frequent aspiration pneumonia eventually lead to chronic lung disease.
- *Dysautonomic crisis* can be triggered by emotional and physical stress; are associated with increased circulating catecholamines; present as prolonged periods of nausea and vomiting.
- *Vasomotor and cardiovascular* symptoms include erythematous skin blotching, hyperhidrosis, hypertension and tachycardia. It is now appreciated that FD is a disorder in which there is inability to modulate sympathetic activity and to release vasopressin by baroreflex-mediated stimuli. Therefore, patients exhibit profound and rapid hypotension without compensatory tachycardia with positional change.

Management and Prognosis
The mainstay of management remains preventative, symptomatic and supportive; includes measures to prevent dryness in eyes, fundoplication with gastrostomy to provide nutrition and avoid risk of aspirations, use of benzodiazepines and clonidine to control vomiting and the dysautonomic crisis, and fludrocortisone and midodrine to manage cardiovascular liability. Despite improved supportive measures only about 50% of the patients reach adulthood.

HSAN IV (Congenital Insensitivity to Pain with Anhidrosis [CIPA])
Hereditary sensory and autonomic neuropathies type IV is caused by mutations in the neurotrophic tyrosine kinase receptor type1 (*NTRK1*) gene. These are loss of function mutations, leading to impaired signal transduction at the nerve growth factor (NGF) receptor and poor survival of the nociceptive sensory and sympathetic neurons. Sural nerve biopsies show normal myelinated nerve fibers but unmyelinated fibers are absent. Skin biopsy shows deficient C and Aδ fibers in the epidermis and hypoplastic sweat glands without innervation.

Clinical Features
Anhidrosis causes episodic fevers and hyperthermia that is one of the earliest sign of the disorder. Anhidrosis also contributes to the thick skin, dystrophic nails, and reduced scalp hair. There are no cardiovascular symptoms in early childhood. Hyperactivity, severe learning problems are frequently present. Dysautonomic crisis and gastrointestinal dysmotility are not seen and emotional tearing is normal. However, the insensitivity to pain is significant leading to self-mutilation and autoamputation. There is poor healing of ectodermal structures, skin and bone.

Management
Prevention of hyperthermia and injuries are mainstay of management of HSAN-IV patients.

NEUROTRANSMITTER DISORDERS AND DOPAMINE-BETA-HYDROXYLASE DEFICIENCY
Dopamine-beta-hydroxylase (DbH) deficiency is an autosomal recessive disorder that affects catecholamine levels and control on autonomic functions. The enzyme DbH is required for conversion

of dopamine (DA) to norepinephrine (NE) so loss of DbH leads to reduced NE and accumulation of dihydroxyphenylalanine, DA, and its metabolites. As DbH is located predominantly in the adrenal medulla, clinical features of DbH deficiency are consistent with normal parasympathetic and sympathetic cholinergic function but reduced sympathetic noradrenergic function and adrenomedullary failure. This results in cardiovascular symptoms and orthostatic hypotension. In the perinatal period, DbH deficiency presents with vomiting, dehydration, hypotension, hypothermia, and hypoglycemia. By adolescent age, patients present with ptosis of the eyelids and profound orthostatic hypotension. The biochemical tests show minimal or undetectable plasma NE and epinephrine levels with a 5–10-fold elevation of plasma DA level. Treatment is symptomatic; L-threo-3, 4-dihydroxy phenyl serine (droxidopa, DOPS), which is converted peripherally directly into NE is used to improve orthostatic hypotension.

RESPIRATORY AND AUTONOMIC DISORDERS OF INFANCY, CHILDHOOD, AND ADULTHOOD

Most severely affected respiratory phenotypes within respiratory and autonomic disorders of infancy, childhood, and adulthood occur in CCHS and rapid-onset obesity, with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD). CCHS and ROHHAD are discussed here briefly.

Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong condition wherein control of breathing is abnormal and patients present with symptoms of alveolar hypoventilation. The severity of hypoventilation varies and most patients present in the neonatal period though late onset is also known. Central alveolar hypoventilation is diagnosed when the arterial PCO_2 is more than 45 mm Hg during wakefulness, due to decreased central ventilatory drive.

Congenital central hypoventilation syndrome is caused by a defect in the *PHOX2B homeobox* gene and inheritance is autosomal dominant. This gene maps to chromosome 4p12 and encodes for a transcription factor that plays a role in the regulation of neural crest cell migration and development of the ANS.

Diagnostic criteria The diagnosis of CCHS requires the following criteria as proposed by Keens and Hoppenbrouwers:
- Persistent evidence of hypoventilation during sleep [$PaCO_2$ > 60 mm Hg (8 kPa)]. Central alveolar hypoventilation
- Onset of symptoms usually in the first year of life
- Absence of primary pulmonary or neuromuscular disease or identifiable brainstem lesion
- No evidence of primary heart disease.

Clinical presentation Infants with CCHS typically present in the newborn period with episodes of cyanosis or apnea, and most require mechanical ventilation immediately after birth. Occasionally, infants may present in the first few months of life with acute life-threatening events. During sleep, infants will appear to have regular, shallow respiratory movements, with periods of central apnea. In some infants, hypoventilation may be seen during both wakefulness and sleep. Children with CCHS can also present with symptoms of end-organ damage from chronic, unrecognized hypoxemia and hypercarbia, such as cor pulmonale, seizures or developmental delay.

Other manifestations Diseases of neural crest origin, also known as neurocristopathies, are often associated with CCHS. These lesions result from aberrations in the migration, growth or differentiation of neural crest cells and include Hirschsprung's disease, which is

present in approximately 16% of cases of CCHS. Tumors of neural crest origin, including mediastinal or abdominal neuroblastoma or ganglioneuromas, may occur in 5% patients of CCHS. Other symptoms of AD seen in CCHS include temperature instability, excessive sweating, and swallowing dysfunction.

Diagnosis and management Congenital central hypoventilation syndrome has many differential diagnoses, neurological, respiratory, cardiac and metabolic diseases should be ruled out by relevant investigations. Genetic testing should be performed for the *PHOX2B* screening test which will identify the mutation in 95% of CCHS cases. The goal of treatment for CCHS is to ensure adequate oxygenation and ventilation during both wakefulness and sleep so as to avoid long-term neurological complications and *cor pulmonale* related to hypoventilation. Tracheostomy with positive pressure ventilation, noninvasive ventilation and diaphragmatic pacing has been tried in various combinations with reasonable success. Ventilators are adjusted to maintain CO_2 levels ideally between 30 mm Hg and 40 mm Hg and SpO_2 above 95%. Early individualized home ventilation and monitoring plan with periodic reviews is key strategy in patient management. Mortality in these patients remains high; the main causes of death include *cor pulmonale*, pneumonia and aspiration.

Rapid-onset Obesity, with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Children with ROHHAD typically present between the ages of 1.5 years and 9 years with rapid-onset obesity, followed by an evolving presentation that includes hypothalamic dysfunction, such as water imbalance, resulting in hyponatremia or hypernatremia, hyperprolactinemia and altered onset of puberty.

Criteria for preliminary diagnosis of ROHHAD include:
- Onset of alveolar hypoventilation after the age of 1.5 years
- Evidence of hypothalamic dysfunction, as defined by more than or equal to 1 of the following findings: rapid onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotropin deficiency, or delayed or precocious puberty.

Nearly half of the children will experience a cardiorespiratory arrest. Typical presentation occurs after an intercurrent viral infection, then obstructive sleep apnea and hypoventilation are noted. Other symptoms of autonomic dysregulation include: low body temperature, cold hands and feet, severe bradycardia, and decreased pain perception. Approximately 40% of children with ROHHAD demonstrate a tumor of neural crest origin; which is often found in the adrenal gland but can also be found in the paraspinal area along the sympathetic chain. As there is no current genetic testing available for this disorder, the diagnosis of ROHHAD is based on the clinical presentation, the related clinical features, and the documented absence of other potentially confounding diagnoses, including ruling out late onset CCHS with *PHOX2B* testing.

SECONDARY CAUSES OF AUTONOMIC DYSFUNCTION

Guillain-Barré Syndrome

Autonomic dysfunction is a common and important complication in GBS and occurs in approximately two-thirds of patients and is often associated with a variety of derangements including cardiovascular, vasomotor, or dysfunctions in both the sympathetic and parasympathetic systems. Very rare pure autonomic variants of GBS, defined as pandysautonomia are also reported. One

pediatric study showed 50% prevalence of AD in mild childhood GBS and the prevalence of AD was much more common in the AIDP subtype than in the AMAN subtype. Up to 90% patients with moderate or severe GBS have AD. Sinus tachycardia is one of the most frequent manifestations and hypertension and postural hypotension are also common. HRV analysis is noninvasive and easily applicable, as it does not require any motor task. In GBS patients, reduced HRV has been reported.

HIV Infection
Neurologic complications of HIV are well-characterized in the central and peripheral nervous systems but not in the ANS, due to the complexities of measuring autonomic function in medically ill populations. AD is common in HIV, can be measured with an autonomic reflex screen, and is associated with distal symmetric polyneuropathy (DSP) but not with signs of CNS disease. Autonomic dysfunction was present in up to 90% of participants with severe DSP and in only 30% of participants with little or no DSP. Pathogenesis of DSP and autonomic involvement is not well-understood and can be seen despite treatment.

Diabetic Autonomic Neuropathy
Diabetic autonomic neuropathy (DAN) is among the least recognized complications of diabetes mellitus despite its significant negative impact on survival and quality of life in people with diabetes. DAN can involve the entire ANS. DAN may be either clinically overt or subclinical with one or more organ system dysfunction (e.g., cardiovascular, gastrointestinal, sudomotor, or pupillary). Clinically symptomatic autonomic neuropathy generally occurs many years after diabetes onset, though subclinical autonomic dysfunction can occur within a year of diagnosis in type II diabetes and within 2 years in patients with type I diabetes. Because of its association with adverse outcomes, including cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN. Reduced HRV seen in diabetic patients is suggestive of CAN. Gastrointestinal and pupillary dysfunctions are also common. Strict glycemic control is important for primary prevention. In future, gene therapy and pancreatic transplant will play important role in prevention of such complications.

MORE ON THIS TOPIC

Axelrod FB, Chelimsky GG, Weese-Mayer DE. Pediatric autonomic disorders. Pediatrics. 2006;118:309-21.

Axelrod FB. Genetic autonomic disorders. Semin Pediatr Neurol. 2013;20:3-11. Freeman R. Autonomic peripheral neuropathy. Lancet. 2005;365: 1259-70.

Kuntz NL, Patwari PP. Laboratory evaluation of pediatric autonomic disorders. Semin Pediatr Neurol. 2013;20:35-43.

Moodley M. Clinical approach to syncope in children. Semin Pediatr Neurol. 2013;20:12-7.

Rand CM, Patwari PP, Carroll MS, Weese-Mayer DE. Congenital central hypoventilation syndrome and sudden infant death syndrome: disorders of autonomic regulation. Semin Pediatr Neurol. 2013;20:44-55.

IN A NUTSHELL
1. The ANS innervates every organ in the body, and autonomic disorders are pervasive and encompass a broad spectrum of symptoms.
2. The list of pediatric disorders with autonomic dysfunction, primary or secondary, is increasing every day and there is strong need to suspect and recognize them.
3. Cardiovascular system autonomic dysfunction is important cause of morbidity and mortality in many chronic illnesses.
4. Diagnostic facilities should be utilized for better understanding of pathophysiology and to plan out treatment.
5. It should be suspected in patients of diabetes mellitus, all disorders associated with sensory neuropathy and small fiber neuropathy.
6. Syncope in children is of neurocardiogenic type and is mostly benign.

Section Editors PSN Menon, Vijayalakshmi Bhatia

Chapter 44.1

Principles of Endocrinology and Hormone Action

Khalid Hussain

The endocrine system consists of glands that synthesize and secrete hormones. A hormone is a specific chemical messenger molecule. These hormones are then carried in the blood stream to their target organ/s. Hormones allow communication between different organs and tissues. The hypothalamus, pituitary gland, thyroid gland, adrenal glands, parathyroid glands, the pancreas, ovaries, testes and the pineal gland constitute the main endocrine glands in the body **(Fig. 1)**. The gastrointestinal tract, heart, kidneys and adipose tissue can also produce hormones although these organs are not classical endocrine glands. Endocrine glands by secreting hormones regulate many physiological and biochemical aspects (such as growth, metabolism, reproduction, lactation, development and adaptation to stress) and help to maintain homeostasis.

PHYSIOLOGICAL AND BIOCHEMICAL ACTIONS OF HORMONE

A hormone is a chemical messenger that is synthesized and secreted by endocrine glands. It is then transported in the blood stream so that it can reach its target tissue/s where it will initiate its physiologic action. Hormones serve as a major form of communication between different organs and tissues. Hormones regulate many physiological and biochemical functions and help to maintain homeostasis. Although typically hormones are released into the blood stream and have their effect on a distant target organ, hormones may also have a paracrine action (affect the function of neighboring cells) or autocrine action (effects on the same cells that secreted the hormone).

Most hormones are synthesized as prohormones (proinsulin for example) which are then converted into the active form. In the circulation carrier proteins are able to bind to some hormones and help with their transport. However, only the free hormone (that fraction of the total hormone level which is unbound to any carrier protein) is active and available to bind to specific receptors to induce its effects.

Some hormone are water soluble (protein hormones like insulin) and are thus readily transported through the circulatory system whereas other hormones (steroid and thyroid hormones), are water insoluble and need to bind to plasma glycoproteins (e.g., thyroxine-binding globulin). Virtually all hormones have a pulsatile secretion pattern which is important for hormone action and tissue sensitivity.

The biochemical and physiologic effects of a hormone on its target tissue will depend on the concentration of the hormone in
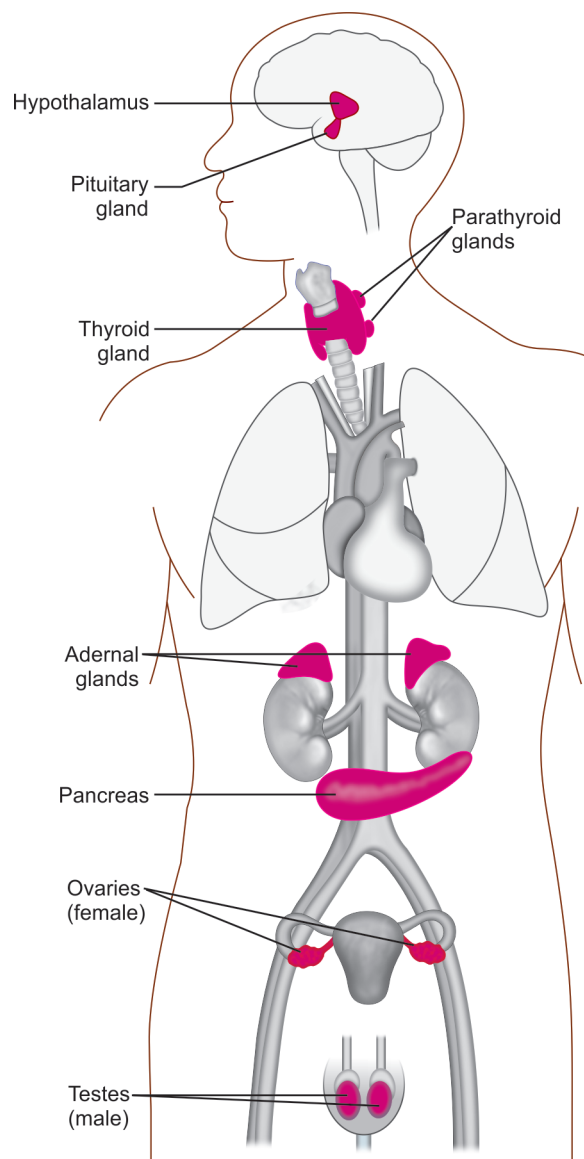
Figure 1 Summary of the major endocrine glands in the body. The major endocrine glands include the hypothalamus, pituitary gland, thyroid gland, adrenal glands, parathyroid glands, the pancreas, ovaries, testes and the pineal gland

the circulation. Three factors (rate of production, rate of delivery and rate of degradation and elimination) regulate the levels of a hormone at the target tissue. Positive and negative feedback circuits (loops) play a role in regulating the synthesis and secretion of a hormone. Hormone elimination is characterized by the half-life of a hormone.

CATEGORIES OF HORMONES

Hormones can be chemically classified into three main categories—the hormones derived mostly from peptides and proteins; hormones derived from cholesterol and the amino acid derivatives.

Peptides and Proteins Hormones

Peptide hormones (such as thyrotropin-releasing hormone, TRH and vasopressin) are made of chains of amino acids. Protein hormones are made of longer chain of amino acids and examples include insulin and growth hormone (GH). Some protein hormones have carbohydrate side-chains (glycoproteins) attached and examples include follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH). Some protein hormones have to be synthesized as prohormones (e.g., proinsulin to insulin), which will only become active when they undergo proteolytic cleavage so that the active mature form of the hormone can be generated. The endoplasmic reticulum (ER) and the Golgi apparatus play important roles in synthesizing and transporting hormones so that they can be packaged into secretory vesicles for export.

Steroid Hormones

Cholesterol is important for the synthesis of steroid hormones. Testosterone and cortisol are examples of steroid-derived hormones. The first and rate-limiting step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone. Once secreted, steroid hormones may be bound to albumin or by specific binding proteins. This binding to albumin or by specific binding proteins will alter the elimination and half-life of the hormone.

Amino Acid Derivatives

The amino acid tyrosine is a constituent of thyroid hormones and catecholamines. The amino acid tryptophan is used in the synthesis of serotonin and the pineal hormone melatonin. Thyroid hormones have a circulating half-life of the order of a few days and are inactivated by intracellular deiodinases. On the other hand, catecholamines are rapidly degraded, with circulating half-lives of only a few minutes.

FEEDBACK CONTROL OF HORMONE PRODUCTION

Negative feedback describes a feedback loop by which a hormone can regulate its own secretion. Negative feedback loops allow the maintenance of hormone levels within an appropriate physiological range. An example of a negative feedback loop is the regulation of thyroid hormone secretion **(Fig. 2)**.

Thyroxine and triiodothyronine (T4 and T3) are produced and secreted by the thyroid gland. The secretion of these two hormones is regulated by TSH which is released by specialized cells in the anterior pituitary gland called the thyrotropes. The function of the thyrotropes is in-turn controlled by cells located in the hypothalamus which secrete TRH. When the blood levels of T4 and T3 are above the physiological range they inhibit the secretion of TRH which in turn will reduce the secretion of TSH thus lowering the blood levels of T4 and T3.

HORMONE RECEPTORS

Hormone receptors are located either on the surface of the cell or within the cell, depending on the type of hormone. The binding of a hormone to its receptor triggers a cascade of reactions within the cell that regulates its function. Hormones can act as agonists where they bind their receptors and induce (augment) all the
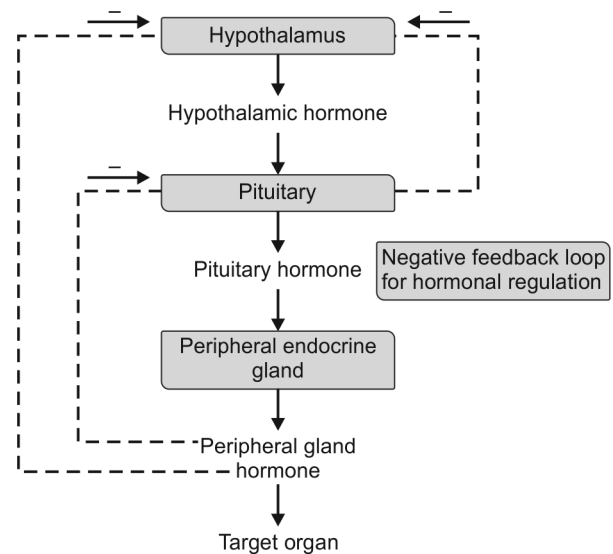
Figure 2 An example of a negative feedback loop in hormonal control

post-receptor signaling events. For a given receptor, different agonists can have dramatically different potencies. Some hormones can act as antagonists where they bind the receptor and block binding of the agonist and prevent the triggering of the intracellular signaling events.

MECHANISMS OF ACTION OF HORMONES

There are two main classes of receptors, those located on the cell membrane (e.g., the insulin receptor) and those located in the cytoplasm (e.g., the glucocorticoid receptor). The receptors on the cell membrane can be classified into four main groups:

1. G-protein-coupled seven-transmembrane domain receptors [e.g., those for luteinizing hormone (LH), FSH, and TSH]
2. Single transmembrane domain growth factor receptors (insulin, insulin-like growth factor)
3. Cytokine receptors (cytokines, GH, prolactin)
4. Guanylyl cyclase-linked receptors (natriuretic peptides related to guanylyl cyclase second messenger system).

These receptors generally function via intracellular second messengers, including cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol 1,4,5-trisphosphate (IP3) and the calcium (Ca^{2+})-calmodulin system.

G-Protein-Coupled Receptor Signaling

G-protein-coupled receptors (GPCRs) are a large protein family of receptors that play important roles in signal transduction pathways. Hormone binding to GPCR induces a conformational change, thus allowing it to act as a guanine nucleotide exchange factor **(Fig. 3)**. The GPCR triggers activation of the associated G-protein by allowing the exchange of its bound guanosine diphosphate (GDP) for a guanosine triphosphate (GTP). The α subunit of the G-protein together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type (Gαs, Gαi/o, Gαq/11, Gα12/13). The α-subunit possesses an intrinsic GTPase activity and hydrolyses GTP to GDP. This terminates the signaling cascade and α and $\beta\gamma$ reassociate.

Signaling via the Receptor Tyrosine Kinases

Hormones can also signal via receptor tyrosine kinases (RTK). RTKs are part of the larger family of protein tyrosine kinases, encompassing the RTK proteins which contain a
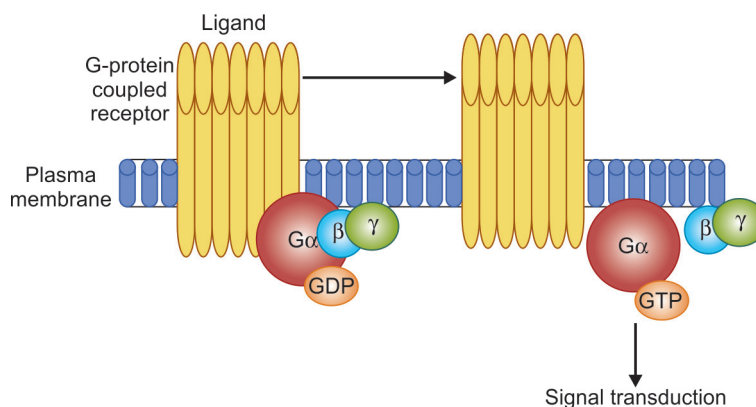
Figure 3 The G-protein-coupled receptors (yellow) triggers activation of the associated G-protein by allowing the exchange of its bound guanosine diphosphate for a guanosine triphosphate. The α subunit of the G-protein (red) together with the bound guanosine triphosphate, can then dissociate from the β and γ subunits (blue and green) to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type (Gαs, Gαi/o, Gαq/11, Gα12/13). The α-subunit possesses an intrinsic GTPase activity and hydrolyses guanosine triphosphate to guanosine diphosphate

transmembrane domain, as well as the nonRTKs which do not possess transmembrane domains. When hormones bind to RTK, dimerization of the receptor occurs and this then stimulates the receptor's intrinsic protein-tyrosine kinase activity. This stimulates a signal-transduction cascade which brings about changes in gene expression and protein synthesis. Some RTKs are themselves protein kinases and become active (by phosphorylation) when the hormone binds. Insulin is an example of a hormone whose receptor is a tyrosine kinase.

Signaling via the Nuclear Receptors
Thyroid hormone and steroid hormone receptors are examples of receptors which are located inside the cell (cytoplasm or nucleus). They function as transcription factors by binding to a ligand. When the hormone binds to the receptor, it becomes competent to bind to DNA sequences **(Fig. 4)**. The hormone-receptor complex then attaches to the promoter regions of responsive genes and stimulates (sometimes inhibits) transcription from those genes.

Second Messengers
Second messengers are intracellular signaling molecules which when released initiate physiological changes such as proliferation, differentiation, migration, survival, and apoptosis. These second messengers function to amplify the initial signal. There are three major classes of second messengers: cyclic nucleotides (e.g., cAMP and cGMP), inositol trisphosphate (IP3) and diacylglycerol (DAG) and calcium ions (Ca^{2+}).

Cyclic AMP Second Messenger Systems
Cyclic adenosine monophosphate is a nucleotide generated when the enzyme adenylate cyclase acts on ATP. The cAMP concentration inside the cell can increase or decrease depending on the hormonal signal. When the cAMP concentration level increases it activates a cAMP-dependent protein kinase called protein kinase A. When protein kinase A is activated, it phosphorylates several other proteins which further trigger the signal cascade.

Inositol Trisphosphate and Diacylglycerol
Some hormones such as TSH and vasopressin function by binding to GPCRs that then activate the intracellular enzyme phospholipase C (PLC). PLC enzyme hydrolyses phospholipids, specifically phosphatidylinositol-4,5-bisphosphate (PIP2) which is found in the inner layer of the plasma membrane. Hydrolysis of PIP2 yields
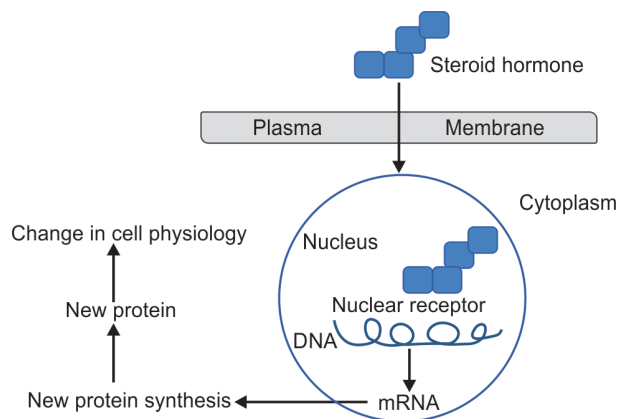
Figure 4 An example of hormone signaling via nuclear receptors. The hormone-receptor complex binds to promoter regions of responsive genes and stimulates genes. The binding of the hormone to the receptor leads to a conformational change in the receptor and the receptor becomes competent to bind DNA. Activated receptors bind to hormone response elements, which are short specific sequences of DNA which are located in promoters of hormone-responsive genes. Transcription from those genes to which the receptor is bound is affected

two products, DAG and inositol-1,4,5-trisphosphate (IP3). DAG remains in the inner layer of the plasma membrane and recruits protein kinase C, a calcium-dependent kinase that phosphorylates many other proteins that bring about the changes in the cell. IP3 is a soluble molecule that diffuses through the cytoplasm and binds to receptors on the endoplasmic reticulum causing a rise in the intracellular calcium level.

Calcium Ions (Ca^{2+}) as Second Messengers
Calcium ions are important intracellular messengers and play key roles in numerous physiological processes. Calcium levels in the cytoplasm increase in response to numerous signals. The increase in the intracellular calcium level triggers a number of physiological processes including exocytosis (e.g., insulin secretion), release of neurotransmitters at synapses and muscle contraction. Calcium levels in the cytoplasm are normally maintained in the low (10–100 nM) range. In order to keep the calcium level low in the cytoplasm, calcium is actively pumped

from the cytoplasm to the extracellular space and into the ER, and sometimes in the mitochondria. Some proteins in the cytoplasm can act as buffers to bind Ca^{2+}.

OVERVIEW OF ENDOCRINE GLANDS AND THEIR FUNCTIONS

The endocrine glands in the body include the hypothalamus, pituitary gland, thyroid gland, adrenal glands, parathyroid gland, the pancreas, ovaries and testes and the pineal gland.

Hypothalamus

The hypothalamus is a part of the brain located superior and anterior to the brainstem and inferior to the thalamus. It plays a key role controlling the function of the various endocrine glands especially the pituitary gland. Specialized cells in the hypothalamus (neurosecretory cells) synthesize and secrete several key hormones. These include the growth hormone-releasing hormone (GHRH), growth hormone-inhibiting hormone (GHIH), corticotropin-releasing hormone (CRH), TRH and gonadotropin-releasing hormone (GnRH). The hypothalamus also is involved in synthesizing the hormones oxytocin and antidiuretic hormone (ADH).

These hormones which are released from the hypothalamus control the function of the anterior pituitary gland. For example GHRH will stimulate whereas GHIH will inhibit GH secretion.

With regard to the thyroid axis, the hormone TRH stimulates the anterior pituitary gland to secrete TSH. The secretion of FSH and LH is controlled by GnRH and adrenocorticotropic hormone (ACTH) secretion is regulated by CRH. The hypothalamus produces the hormones oxytocin and ADH; however these have to be transported to the posterior pituitary. In the posterior pituitary these hormones are stored and then released in response to stimuli.

Pituitary Gland

The pituitary gland (also known as the hypophysis) is situated in the small depression of the sphenoid bone called the sella turcica and is made up of two completely separate structures: the posterior and anterior pituitary glands. The anterior pituitary gland is the true glandular part of the pituitary gland. The function of the anterior pituitary gland is controlled by the releasing and inhibiting hormones of the hypothalamus (see above).

The anterior pituitary produces six important hormones: TSH is a tropic hormone responsible for the stimulation of the thyroid gland. ACTH stimulates the adrenal cortex to produce cortisol. FSH stimulates the follicle cells of the gonads to produce gametes—ova in females and sperm in males. LH stimulates the gonads to produce the sex hormones—estrogens in females and testosterone in males. Human GH affects many target cells throughout the body by stimulating their growth and regulating metabolism. Prolactin (PRL) stimulates the mammary glands of the breast to produce milk.

The posterior pituitary is actually an extension of the hypothalamus and contains axons of some of the neurosecretory cells. These neurosecretory cells secrete two hormones in the hypothalamus that are transported, stored and released by the posterior pituitary. Oxytocin triggers uterine contractions during childbirth and the release of milk during breastfeeding. ADH prevents water loss in the body by increasing the re-uptake of water in the kidneys and reducing blood flow to sweat glands.

Thyroid Gland

The thyroid gland is a butterfly-shaped gland located at the base of the neck and wrapped around the lateral sides of the trachea.

The thyroid gland synthesizes and secretes thyroid hormones as well as calcitonin. Thyroxine (T4) is the main hormone secreted by the thyroid gland. In the peripheral tissues T4 is converted to the biologically active triiodothyronine (T3). T4 and T3 have numerous physiological roles and play a particularly crucial role in brain maturation during fetal development.

Calcitonin (also known as thyrocalcitonin) is a 32-amino acid linear polypeptide hormone that is produced in humans by the parafollicular cells (also known as C-cells) of the thyroid gland. Calcitonin secretion is regulated by changes in the calcium level and if the serum calcium level rises above a certain point calcitonin will be released. Calcitonin lowers the serum calcium level by increasing the amount of calcium that gets into the bones.

Adrenal Glands

The adrenal glands are anatomically located above the two kidneys. They are made up of two layers—outer adrenal cortex and the inner adrenal medulla—with each one having different functions. The outer cortex mainly produces cortisol, aldosterone and androgens, while the inner medulla produces adrenaline and noradrenaline.

Glucocorticoids have many diverse functions, including the breakdown of proteins and lipids to produce glucose and function to reduce inflammation and immune response. Mineralocorticoids are a group of hormones that help to regulate the concentration of mineral ions in the body. Androgens, such as testosterone, are produced at low levels in the adrenal cortex to regulate the growth and activity of cells that are receptive to male hormones. The adrenal medulla produces the hormones adrenaline and noradrenaline under stimulation by the sympathetic division of the autonomic nervous system. Adrenaline and noradrenaline effects include increased heart rate and blood pressure, blood vessel constriction in the skin and gastrointestinal tract, blood vessel dilatation in skeletal muscles, bronchiole dilatation, and decreased metabolism, all of which are characteristic of the fight-or-flight response. Release of catecholamines is stimulated by nerve impulses, and receptors for catecholamines are widely distributed throughout the body.

The Pancreas

The pancreas is an endocrine gland producing several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide. The part of the pancreas with endocrine function is made up of clusters of pancreatic tissue called islets of Langerhans. Within the islet of Langerhans four main cell types exist namely β-(beta) cells which secrete insulin (decrease glucose in blood), α-(alpha) cells which secrete glucagon (increase glucose in blood), Δ-(delta) cells which secrete somatostatin (regulates/stops α and β cells) and PP-cells which secrete pancreatic polypeptide.

Gonads

The gonads—ovaries in females and testes in males—produce the sex hormones (testosterone and estrogen). Testosterone and estrogen play important roles in determining the secondary sex characteristics of males and females. In males the testes produce the male hormone, testosterone which is required for pubertal development. Testosterone also has many effects on other body systems including the muscles, bones, sex organs, and hair follicles. Testosterone causes growth and increases in strength of the bones and muscles, including the accelerated growth of long bones during adolescence. During puberty, testosterone controls the growth and development of the sex organs and body hair of males, including pubic, chest, and facial hair.

The ovaries are located in the pelvic body cavity lateral and superior to the uterus in females. The ovaries produce the female sex hormones progesterone and estrogens. Progesterone plays an important role during ovulation and pregnancy where it helps to support the development of the uterus and fetus. Estrogens regulate pubertal development (breast, uterine development, growth of pubic and axillary hair in the female). During adolescence estrogen plays an important role in controlling the growth of bones and thus regulating height.

The Parathyroid Glands

The parathyroid glands are small glands, usually four in number and are situated on the posterior aspect of the thyroid gland. The parathyroid glands synthesize and secrete parathyroid hormone (PTH), which regulates calcium ion homeostasis. When calcium levels drop below a certain level PTH is released from the parathyroid glands. PTH stimulates the osteoclasts to break down the calcium containing bone matrix to release free calcium ions into the bloodstream. PTH also triggers the kidneys to return calcium ions filtered out of the blood back to the bloodstream so that it is conserved.

The Pineal Gland

The pineal gland is located in the brain and produces the hormone melatonin. This is a serotonin derivative and plays an important role in determining sleep patterns.

Nonclassical Endocrine Glands

Several other nonendocrine organs produce hormones such as adipose tissue which produces leptin, the heart which produces the hormone atrial natriuretic peptide in response to high blood pressure levels and the placenta produces several hormones that help to maintain pregnancy.

IN A NUTSHELL

1. The hypothalamus, pituitary gland, thyroid gland, adrenal glands, parathyroid glands, the pancreas, ovaries, testes and the pineal gland constitute the main endocrine glands in the body.
2. Negative feedback describes a feedback loop by which a hormone can regulate its own secretion. It allows the maintenance of hormone levels within an appropriate physiological range.
3. Hormone receptors are either located on the cell membrane (e.g., the insulin receptor) or the cytoplasm (e.g., the glucocorticoid receptor).
4. Receptors on the cell membrane function via intracellular second messengers, including cAMP, cyclic GMP (cGMP), inositol 1,4,5-trisphosphate (IP3) and the calcium (Ca^{2+})-calmodulin system.
5. Cytoplasmic receptors function as transcription factors by binding to a ligand.

MORE ON THIS TOPIC

Beato M, Chavez S, Truss M. Transcriptional regulation by steroid hormones. Steroids. 1996;61:240-51.

Boelen A, Kwakkel J, Fliers E. Thyroid hormone receptors in health and disease. Minerva Endocrinol. 2012;37:291-304.

Posner BI, Laporte SA. Cellular signalling: Peptide hormones and growth factors. Prog Brain Res. 2010;181:1-16.

Rochette-Egly C. Nuclear receptors: integration of multiple signaling pathways through phosphorylation. Cell Signal. 2003;15:355-66.

Ronnett GV, Moon C. G proteins and olfactory signal transduction. Annu Rev Physiol. 2002;64:189-222.

Yang W, Xia SH. Mechanisms of regulation and function of G-protein-coupled receptor kinases. World J Gastroenterol. 2006;12:7753-7.

Chapter 44.2
Physiology of Neuroendocrinology

Priyanka Gupta, Vijayalakshmi Bhatia

The interactions taking place between the endocrine and the nervous system, both working together for control of homeostasis in humans, form the basis of neuroendocrinology. The main neuroendocrine glands are the hypothalamus, the pituitary and the pineal. In addition to maintenance of neuroendocrine-peripheral gland axes and endocrine rhythms, modulation of feeding behavior occurs via the neuroendocrine system.

NEURAL CONTROL OVER HORMONE SECRETION

Overall, the nervous system exerts its control over endocrine system in three ways:
1. *Direct autonomic innervation*, e.g., Sympathetic and para-sympathetic innervation of pancreatic islets of Langerhans and sympathetic innervation of adrenal medulla.
2. *Hypothalamic regulation of anterior pituitary* by specific releasing and inhibiting factors reaching via hypothalamic-hypophyseal portal circulation (discussed in detail below).
3. Hypothalamic regulation of posterior pituitary via hypothalamic-hypophyseal neural tract (discussed in detail below).

HYPOTHALAMIC-PITUITARY UNIT

Hypothalamus serves as the primary link between the nervous and endocrine systems by receiving the information regarding external environment (e.g., light, pain, temperature and smell) and internal environment [e.g., blood osmolarity, blood pressure (BP) and blood glucose levels]. With these inputs, hypothalamus exerts a control over both anterior and posterior pituitary as well as on the important brainstem cardiorespiratory, autonomic and limbic outputs. Circadian or diurnal rhythms characteristic of most pituitary hormones are taken care of by suprachiasmatic nucleus in anterior hypothalamus. Beside these roles, it also controls body temperature, thirst, appetite, energy, body fat composition, immunity, behavior, emotional expression, memory and visceral functions. Therefore, the disorders involving hypothalamus may involve a combination of these various functions.

Pituitary gland placed in sella turcica of sphenoid bone at the base of skull, has a glandular component (adenohypophysis) and a neural component (neurohypophysis). Adenohypophysis is subdivided into three distinct parts, i.e., *pars distalis* (anterior lobe), *pars intermedia* (intermediate lobe which is rudimentary in humans) and *pars tuberalis*. Adenohypophysis has five cell types (somatotropes, lactotropes, corticotropes, thyrotropes and gonadotropes) secreting six hormones **(Table 1)**. The neurohypophysis is composed of *pars nervosa* (posterior lobe), infundibular stalk and the median eminence. Due to its unique position in the brain, any increase in the size of pituitary (e.g., tumor) is associated with dizziness due to compression on brain above or vision problems due to compression on optic chiasma below or both.

The secretion of anterior pituitary hormones is controlled by hypothalamus through hypophysiotropic (releasing) and release inhibiting hormones **(Table 1)** released by a subset of parvicellular (small) neuronal cell bodies and also by the feedback from the circulating hormones of the target glands and paracrine and autocrine secretions of the pituitary itself. The posterior pituitary releases two hormones, i.e., ADH (antidiuretic hormone or vasopressin) and oxytocin, which are actually synthesized in the magnocellular (large) cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus respectively. They are released from posterior pituitary in response to stimuli that are primarily detected in the hypothalamus.

MAINTENANCE OF NEUROENDOCRINE AXES

Each neuroendocrine axis maintains its activity at a set point by the integration of hypothalamic stimulation and peripheral hormonal negative feedback action on the pituitary and hypothalamus. The target organ hormone or its biochemical surrogate feeds back on the anterior pituitary and/or hypothalamus. Thus, if the peripheral hormone level falls, the secretion of hypothalamic-releasing hormone and pituitary tropic hormone will increase and vice versa in case of rise in peripheral hormone levels (*long loop feedback*). Anterior pituitary tropic hormones may also affect the synthesis or release their contemporary hypothalamic releasing or release-inhibiting hormone (*short loop feedback*). Hypophysiotropic hormones may inhibit their own synthesis and secretion also (*ultrashort loop feedback*).

ENDOCRINE RHYTHMS

Most endocrine rhythms are *circadian* (that is, synchronized with the day/night cycle). Over these circadian rhythms, *ultradian* secretory bursts (less than a day, i.e., minutes or hours) are superimposed. *Infradian* rhythms have cyclicity longer than 1 day, for example 28 day menstrual cycle. Growth hormone (GH) and prolactin (PRL) are secreted maximum after the onset of sleep. Plasma thyroid stimulating hormone (TSH) is maximum between 9 pm and 5 am and minimum between 4 pm and 7 pm. Levels of adrenocorticotropic hormone (ACTH) and cortisol start rising between 1 am and 4 am, peaking in early morning, falling during

Table 1 Hypothalamic and pituitary hormones

Hypothalamus	*Anterior pituitary hormones*
Anterior pituitary regulating hormones • TRH (thyrotropin-releasing hormone) • GnRH (gonadotropin-releasing hormone) • CRH (corticotropin-releasing hormone) • GHRH (growth hormone-releasing hormone) • Somatostatin (GHRIH, growth hormone release-inhibiting hormone) • Dopamine	• TSH (thyroid stimulating hormone, thyrotropin) • ACTH (adrenocorticotropic hormone, corticotropin) • GH (growth hormone, somatotropin) • FSH (follicle-stimulating hormone) • LH (luteinizing hormone, interstitial cell stimulating hormone) • PRL (prolactin, luteotropic hormone, lactogenic hormone, mammotropin)
Posterior pituitary hormones • ADH (antidiuretic hormone or arginine vasopressin, AVP) • Oxytocin	

the day time, and having a nadir at about midnight. PRL blood levels also peak in early morning hours. Gonadotropin secretion in adolescents is increased in the night.

It is important to understand these rhythms while taking into account the appropriate timing of collection of blood samples for assessment of hormone levels. Since these rhythms are mainly controlled by the hypothalamus, the loss of these rhythms may be the earliest sign of hypothalamic dysfunction.

CLASSIC HYPOTHAMIC-PITUITARY AXES

GHRH, GHRIH and GH

Growth hormone-releasing hormone (GHRH) stimulates secretion of GH and expression of *GH* gene in somatotropes of anterior pituitary. On the other hand, GH release-inhibiting hormone (GHRIH or somatostatin) inhibits secretion of GH and also that of PRL and TSH. Ghrelin, an appetite stimulant secreted from hypothalamus also increases GH secretion, thus coordinating nutrient acquisition with growth. Various physiological states and factors affecting GH secretion are listed in **Table 2**.

The major target organ of GH is liver where it stimulates formation of insulin-like growth factor-1 (IGF-1) forming a part of the hypothalamic-pituitary-hepatic axis. IGF-1 exerts a negative feedback effect on GH secretion both at pituitary and hypothalamic levels. In addition, GH itself exerts negative feedback on release of GHRH. GH also increases somatostatin release.

Dopamine and Prolactin

Among other cells of adenohypophysis, lactotropes are unique in the sense that the production and secretion of PRL is predominantly under inhibitory control of hypothalamus by dopaminergic tracts. Thus, the disruption of pituitary stalk and hypothalamic-hypophyseal portal vessels results in increase in PRL levels unlike a decrease in ACTH, TSH, GH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Dopamine inhibits secretion of TSH and GH also.

As the name suggests the primary function of PRL is to favor lactogenesis, i.e., milk synthesis. It also influences development of mammary glands, reproductive functions and immune responses. Normal basal serum concentration of PRL is similar in men and women, which is increased during pregnancy, lactation and estrogen therapy. Sucking is the most important stimulus for prolactin secretion reflex. Stress, exercises, surgery, fear and stimuli causing arousal and some antihypertensive drugs and tricyclic antidepressants also increase PRL secretion. Thyrotropin-releasing hormone (TRH), angiotensin II, serotonin and opioids are other important PRL releasing factors. Dopamine agonist drugs

such as bromocriptine, somatostatin and gamma-aminobutyric acid (GABA) decrease PRL secretion. Negative feedback control over PRL secretion is mediated by PRL itself acting on the hypothalamus causing increase in dopamine synthesis and release (short loop feedback).

Corticotropin-Releasing Factor and Adrenocorticotropic Hormone

Corticotropin-releasing factor (CRH) causes a prompt release of ACTH and augments the expression of proopiomelanocortin (*POMC*) gene in corticotropes. POMC is cleaved to form β-lipotropin (which can be further cleaved into γ-lipotropin and β-endorphins) and ACTH (which can be further cleaved into α-melanocyte-stimulating hormone and CLIP, i.e., corticotropin-like intermediate peptide in lower vertebrates). CRH also stimulates sympathetic activity, increases BP and activates brainstem reticular activating system causing arousal, which complements the activity of hypothalamic-pituitary-adrenal (HPA) axis when exposed to stress.

Beside physical stresses like injury, infection, fever, surgery, anesthesia and hypoglycemia, psychological stresses like anxiety, fear and depression also stimulate ACTH secretion. ADH and interleukins (particularly IL-1, 2 and 6) also augment ACTH secretion.

Cortisol secreted from adrenal cortex in response to ACTH exerts negative feedback on the pituitary and the hypothalamus. Besides that, ACTH also negatively feeds back over CRH production. However, the hypothalamus has the ability to reset the set point of the HPA axis in response to stress which is obvious by the fact that response to many forms of stress can persist despite negative feedback from the high cortisol levels. Somatostatin, opioids, GABA and brain natriuretic peptide are other inhibitors of ACTH secretion and release.

Thyrotropin-Releasing Hormone and Thyroid Stimulating Hormone

Thyrotropin-releasing hormone from hypothalamus stimulates secretion and synthesis of TSH from thyrotropes of anterior pituitary. It also promotes the secretion and synthesis of PRL. Exposure to cold causes a sharp increase in TRH and TSH secretion. Secretion of TRH and TSH is suppressed by physical stress, starvation and infection. Temperature and the metabolic state also affect TRH secretion. The secretion of TRH and TSH is inhibited by triiodothyronine (T3) and thyroxine (T4) from thyroid gland by a negative feedback. Dopamine, somatostatin and GH also inhibit TSH secretion.

Table 2 Physical states/factors affecting growth hormone secretion

Stimulatory factors	Inhibitory factors
• Infancy and puberty	• Old age
• Slow wave sleep	• REM sleep
• Exercise	• Obesity
• Fasting	• Pregnancy
• Neurogenic and physical stresses	• Hyperglycemia
• Acute hypoglycemia	• Elevated plasma free fatty acids
• Hyperaminoacidemia (arginine, lysine)	• Elevated GH levels
• Hormones: estrogens, testosterone and acute rise in glucocorticoids	• Elevated IGF-1 levels
• Drugs: L-dopa, clonidine, apomorphine	• Chronic rise in glucocorticoids
• Neuropeptides: GHRH, ghrelin, galanin, opioids and melatonin	• Neuropeptides: somatostatin, calcitonin, neuropeptide-Y and CRH
• Neurotransmitters: acetylcholine, serotonin, histamine, GABA	

Abbreviations: REM, rapid eye movement; GHRH, growth hormone-releasing hormone; CRH, corticotropin-releasing hormone; GABA, gamma-aminobutyric acid.

GnRH, LH and FSH

Although, gonadotropin-releasing hormone (GnRH) primarily stimulates secretion of LH and FSH, it stimulates secretion of GH also. The pulsatile secretion and the frequency of pulses of GnRH have important effects on the gonadotropes. Continuous infusion of GnRH downregulates GnRH receptors, thus decreasing the FSH and LH secretion. At a frequency of 1 pulse/hour, GnRH preferentially increases LH secretion. At a slower frequency of 1 pulse/3 hours, GnRH preferentially increases FSH secretion.

Gonadotropin-releasing hormone secretion is influenced by various psychological, emotional and chemical factors. Norepinephrine stimulates; dopamine and endorphins inhibit GnRH secretion. Secretion of LH and FSH is under feedback control of estrogen, progesterone, testosterone, inhibin and activin secreted from gonads. In females, progesterone and testosterone negatively feeds back at the level of hypothalamus and pituitary. At low doses, estrogen also exerts negative feedback on FSH and LH secretion. However, high estrogen levels maintained for 3 days cause a surge in LH and to a lesser extent in FSH secretion. Thus, a positive feedback is observed at the hypothalamus and pituitary. In males, testosterone and estrogen negatively feeds back at the level of pituitary and the hypothalamus. Inhibin inhibits and activin stimulates FSH synthesis and secretion. PRL inhibits LH and FSH secretion by inhibiting GnRH secretion from hypothalamus, which may cause anovulation and amenorrhea in lactating mothers.

Antidiuretic Hormone

Antidiuretic hormone (ADH, also called arginine vasopressin AVP) increases water reabsorption in the distal convoluted tubules and collecting ducts of kidneys and regulates BP by contraction of smooth muscles of vessel walls. ADH increases ACTH secretion also both by its direct action on corticotropes as well as on the hypothalamus for the CRH release. This hormone also facilitates the memory by acting as a neurotransmitter in memory areas of brain.

Increase in plasma osmolarity more than 285 mOsm/L, decreased BP and decreased extracellular fluid (ECF) volume which is sensed by hypothalamus increases ADH secretion. Pain, nausea, vomiting, rise in intracranial pressure, stress, increase in temperature, standing, hypoglycemia and nicotine also increase ADH secretion. Decreased plasma osmolarity, increased ECF volume, decreased temperature, cortisol, thyroxine, atrial natriuretic peptide, ethanol and α-adrenergic agonists decrease ADH secretion.

Oxytocin

Two main physiological functions served by oxytocin in humans are the facilitation of labor and the ejection of milk. During labor, it is released in response to cervical stretch through a neuroendocrine reflex. The receptors for milk ejection reflex are located in and around nipples. Stressful stimuli facilitate oxytocin release. Its secretion is decreased by ethanol.

MODULATION OF FEEDING BEHAVIOR IN HUMANS

Various hormones, neuropeptides and neurotransmitters implicated in the regulation of appetite, satiety and energy expenditure in humans are listed in **Table 3**. They all interact together at the level of paraventricular hypothalamic nucleus (satiety neurons) and lateral hypothalamic nucleus (hunger neurons). Leptin (which is also called adipocytokine) is a cytokine derived from adipocytes signaling the hypothalamus about the degree of adiposity and nutrition. Neuropeptide-Y (NPY) is the principle neuropeptide and a very potent stimulator of food seeking behavior and inhibitor of energy expenditure. Many neurotransmitters and neurochemicals stimulate or inhibit the feeding by increasing or decreasing the release of NPY. **Flow chart 1** gives a simplified overview of how the body's adiposity status itself controls the food seeking behavior. The recently discovered hormone Ghrelin, secreted from the cells of oxyntic glands of stomach, appear to stimulate food intake by reacting with its receptors in hypothalamic neurons that express NPY. Serotonin produces satiety after ingestion of glucose. Gastrointestinal hormones like cholecystokinin and glucagon-like peptide-1 produce satiety by humoral effects, but their local production in brain may also participate in nutrient and calorie regulation.

PINEAL GLAND

Pineal gland, another neuroendocrine structure, is situated in the midline below the third ventricle. A number of functions are attributed to the pineal gland but none of them is decisively attributed to it in humans. Melatonin secreted by pineal gland is believed to be involved in the neurohumoral modulation of human sleep/wake cycle and many circadian rhythms. Although its role in human reproduction is not clear, many experiments show that the pineal gland exerts a negative effect on gonadotropic hormone secretion by pituitary, thus regulating the reproductive axis and the timing of onset of puberty. It is also proposed to slow or reverse the progression of aging. Exposure to continuous light decreases the activity of pineal gland and exposure to continuous darkness increases its activity. The most studied and established therapeutic utility of melatonin in humans is in the treatment of jet lag and circadian rhythm-based sleep disorders.

Table 3 Neurohormones/peptides/transmitters modulating the feeding behavior in humans

Factors promoting food seeking behavior	Factors promoting anorexigenic behavior
• Neuropeptide-Y (NPY) • Agouti-related peptide (AGRP) • Melanin concentrating hormone (MCH) • Norepinephrine • Ghrelin • Orexin A and B (also called hypocretin 1 and 2) • Galanin • Cortisol	• Leptin • Insulin • α-MSH (melanocyte-stimulating hormone) • Cocaine amphetamine regulated transcript (CART) • Serotonin • GLP-1 (glucagon-like peptide-1) • Cholecystokinin (CCK) • Enterostatin • Calcitonin • Bombesin • CRH (corticotropin-releasing hormone) • Urotropin • Interleukin-1β

Flow chart 1 Regulation of feeding behavior at the level of hypothalamus

↑Leptin and insulin secretion in response to increased fat cell mass

Arcuate nucleus: Hypothalamus
Inhibits NPY production
Inhibits AGRP production
Stimulates α-MSH production
Stimulates CART production

Norepinephrine (NE) co-localizes in some of these NPY secretory neurons

| ↓NPY release | ↓AGRP release | ↓NE release | ↑CART release | ↑α-MSH release |

MCH (antagonizes α-MSH at its receptor)

(–) antagonizes α-MSH   (–)

Anorexigenic behavior (Decrease in food intake)

Abbreviations: NPY, neuropeptide-Y; AGRP, Agouti related peptide; NE, norepinephrine; MSH, Melanocyte stimulating hormone; CART, cocaine amphetamine regulated transcript; MCH, melanin concentrating hormone.

IN A NUTSHELL

1. Each endocrine axis has a three-tier configuration. The first tier is represented by hypothalamus, second tier by pituitary and the third tier by peripheral endocrine gland.
2. Anterior pituitary hormone secretion is under control of hypothalamus via various releasing and release-inhibiting hormones as well as the negative/positive feedback mechanisms.
3. Posterior pituitary hormones are synthesized in the hypothalamus and secreted from posterior pituitary in response to various external and internal stimuli detected at the level of hypothalamus.
4. Feeding behavior in humans is controlled at the level of hypothalamus by a complex interplay of various neuro-hormones, neuropeptides and neurotransmitters.
5. Pineal gland is an inseparable component of neuroendocrine system primarily concerned with the maintenance of circadian rhythms.

MORE ON THIS TOPIC

Hall JE. Pituitary hormones and their control by the Hypothalamus. In: Hall JE. Guyton and Hall Textbook of Medical Physiology. 12th ed. Philadelphia: Saunders; 2011. pp. 895-906.

Koeppen BM, Stanton BA. Introduction to the Endocrine system. In: Koeppen BM, Stanton BA. Berne and Levy Physiology. 6th ed. St. Louis, Missouri: Mosby; 2010. pp. 653-63.

Koeppen BM, Stanton BA. Hormonal regulation of energy metabolism. In: Koeppen BM, Stanton BA. Berne and Levy Physiology. 6th ed. St. Louis, Missouri: Mosby; 2010. pp. 664-95.

Koeppen BM, Stanton BA. The Hypothalamus and Pituitary gland. In: Koeppen BM, Stanton BA. Berne and Levy Physiology. 6th ed. St. Louis, Missouri: Mosby; 2010. pp. 706-24.

Low MJ. Neuroendocrinology. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology. 12th ed. Philadelphia: Elsevier Saunders; 2011. pp. 103-74.

Chapter 44.3
Growth Hormone Deficiency and Resistance

Arpita K Vyas, Ram K Menon

During childhood, statural growth is one of the most important physiological processes. It defines the health and nutritional status of a child. Hence, it is vital for clinicians to demonstrate a good knowledge of assessing, interpreting and distinguishing normal from abnormal growth and investigate accordingly. Stature follows a Gaussian distribution and height within 2 standard deviations (SD) of the mean is considered normal height. An individual with a height below 2 SD is considered as having short stature.

A child's height should be measured and plotted on the normal standard (cross sectional or longitudinal) for that population as growth parameters vary by geographical location and ethnicity. Section 19 of this book provides a detailed discussion on growth charts and reference bases available in India, including those developed by Agarwal KN, et al. as well as the World Health Organization (WHO Multicentre Growth Reference Study) growth charts being used around the world, in particular in children below the age of 5 years.

It is important to recognize that deviation from normal growth could be the first manifestation of multiple disease processes both prenatal and postnatal in origin. This chapter focuses on growth hormone deficiency (GHD) and growth hormone resistance (GHR) as causes of poor growth. There is lack of consensus regarding the laboratory definition of GHD mainly because of the controversy surrounding the usefulness of growth hormone (GH) stimulation tests to diagnose GHD. Thus clinical features and auxologic measurements play a key role in the diagnosis of GHD/GHR.

PATHOPHYSIOLOGY OF GROWTH REGULATION

Role of Hypothalamus and Pituitary, and Transcription Factors in Growth

Endocrine regulation of growth is primarily controlled by the hypothalamic–pituitary axis. The arcuate nucleus of the hypothalamus synthesizes growth hormone-releasing hormone (GHRH) which stimulates the production of GH from the somatotrope cells in the anterior pituitary. The hypothalamic arcuate nucleus and periventricular nucleus also synthesize somatostatin which inhibits GH production. Pituitary is the *master gland* which remains central to regulation of growth. It also remains central to the regulation of other endocrine organs in the body including thyroid, adrenals and gonads. The gland is divided into anterior pituitary (adenohypophysis) which embryologically originates from the Rathke's pouch (diverticulum of the primitive oral cavity) and the posterior pituitary (neurohypophysis) originating from the neural ectoderm from the floor of the forebrain and unlike the anterior pituitary has no known function in growth.

The anterior pituitary (adenohypophysis) is functional by 12 weeks of gestation and is responsible for the production of GH **(Fig. 1)**. Multiple transcriptional factors are responsible for formation of the anterior pituitary gland and the determination of the cell lineage within the pituitary, and thus alterations in these transcriptional factors stage cause congenital GHD. The transcriptional factor responsible for the development of the anterior pituitary and optic nerve is the homeobox gene expressed in embryonic stem cells (*HESX1*) and inactivating mutation in
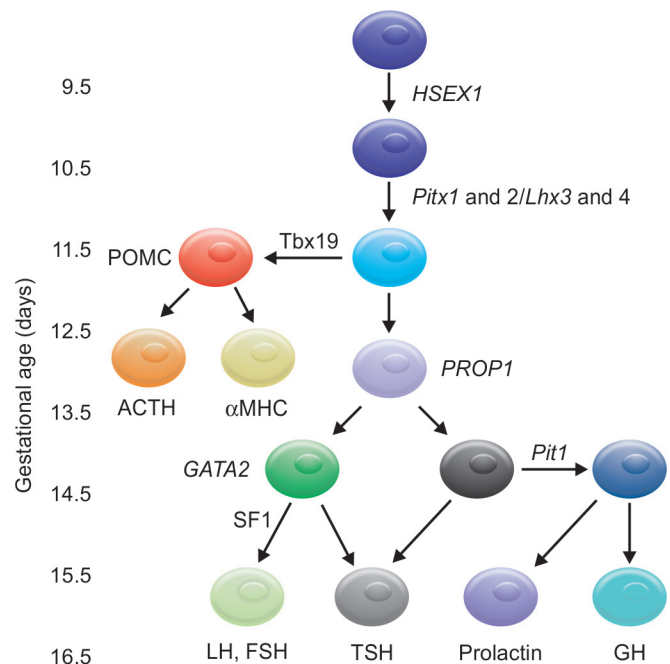
Figure 1 Development of the anterior pituitary gland and transcription factors involved in its differentiation

this gene results in septo-optic dysplasia (de Morsier syndrome), which is associated with deficiency of multiple pituitary hormones including GH. Other key transcription factors responsible for the development of the anterior pituitary include LHX3, LHX4, PTX2, and SOX3. PROphet of Pit1 (*PROP1*) is required for the initial determination of the pituitary cell lineage, including gonado-trophs. *Pit1* (also known as POU1F1) is responsible for differentiation of the cell lineage into thyroid-stimulating hormone (TSH), prolactin (PRL) and GH producing cells. Hence, inactivating mutation in the *PROP1* gene will not only lead to GHD but also lead to adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and TSH deficiencies, whereas inactivating mutation in *Pit1* will lead to TSH, PRL and GHD and spare the gonadotropes and corticotropes.

Growth Hormone Production, Secretion and Action (Fig. 2)

Growth hormone was isolated from human pituitary gland in 1956 by Li and Papkoff and the biochemical structure was defined in 1972. Human GH is a single chain 191 amino acid 22 kD protein and shares structural homology with PRL and placental lactogen and human GH variant. The gene coding for GH is present on chromosome 17. GH is secreted in a pulsatile manner and regulated by hypothalamic peptides including GHRH and somatostatin [somatotropin release inhibitory factor, (SRIF)]. The action of the GHRH receptor (G-protein receptor) on the somatotropes is dependent on the stimulation of adenylate cyclase. Somatostatin is secreted in response to the timing and amplitude of GH. Its binding to its receptor inhibits the adenylate cyclase activity and GH secretion. Neuropeptides (serotonin, histamine, norepinephrine, dopamine, acetylcholine, γ-aminobutyric acid, thyroid-releasing hormone, vasoactive intestinal neuropeptide-Y, vasopressin, corticotropin-releasing hormone and galanin) are also involved in the regulation and release of the hypothalamic factors, GHRH and somatostatin. The regulation of GH secretion by these neuropeptides forms the basis of various GH stimulation
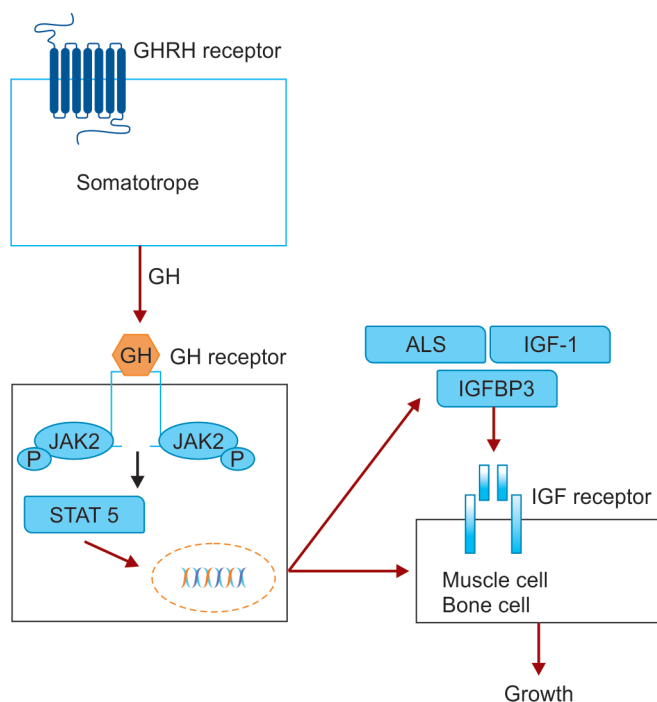
Figure 2 Growth hormone secretion and action

tests employed in evaluation of GHD. GH secretion can also be affected by nonpeptide hormones like androgens, estrogen, thyroxine and glucocorticoid.

After secretion, GH binds to its receptor on the target organ. The gene for the GH receptor is present on chromosome 5. The receptor belongs to the class 1 cytokine receptor family and GH after binding to the receptor stimulates phosphorylation of downstream protein Janus kinase 2 (JAK2) and a cascade of phosphorylation (e.g., STAT 5b) and dephosphorylation events that ultimately results in increased transcription of target genes. Hence, a mutation in receptor gene or the various components of the downstream pathway can lead to GHR leading to poor growth.

Growth hormone also mediates the formation and secretion of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 is the principal mediator of the growth promoting effects of GH. IGF-1 circulates in blood bound to a family of binding proteins termed IGF binding proteins (IGFBP). There are six structurally related proteins in this group. IGFBP3 binds 75–90% of all IGF-1 present in circulation in a large heterotrimeric complex with a third protein, the acid labile subunit (ALS). ALS helps stabilize the complex and extends the half-life of IGF-1 in circulation. The remaining IGF-1 is bound to IGFBP1 whose concentration is controlled by nutritional status and IGFBP2 whose concentration is controlled by the amount of IGF-1 in circulation. IGF binds to the type 1 IGF receptor on target organs. The type 1 IGF receptor shares similarity with the insulin receptor but has higher affinity for IGF-1 and IGF-2 over insulin. On binding to its receptor IGF-1 activates tyrosine kinase with phosphorylation of downstream substrates and activation of discrete cellular pathways leading to specific biological actions.

GROWTH HORMONE DEFICIENCY

Epidemiology
Although data on incidence and prevalence of GHD are scarce, short stature due to GHD has been reported to occur in estimated 1/4,000–1/10,000 children depending on geographical distribution and the criteria used to diagnose the condition. Most cases of GHD are sporadic occurring as a result of developmental anomalies or

Table 1 Etiology of growth hormone deficiency

Congenital	*CNS malformations* • Holoprosencephaly/anencephaly • Pituitary aplasia/hypoplasia • Thin or absent pituitary stalk • Septo-optic dysplasia • Cleft lip and palate • Empty sella syndrome *Genetic mutations* • GHRH receptor mutation • Pituitary transcription factor mutations: *PTX2, LHX3, PROP1, POU1F1 (Pit-1)* • Growth hormone gene mutation
Acquired	*Trauma*: Head injury, birth trauma *Cranial irradiation*: > 30 Gy predispose to GHD *Brain neoplasm* *Infections/infiltration*: Meningitis, Langerhans histiocytosis, hemochromatosis

cerebral insult. In a small proportion (3–30% in certain studies) of cases, an affected first degree relative suggests a genetic etiology. It is generally accepted that incidence and prevalence of GHD is higher in boys compared to girls.

Etiology
Growth hormone deficiency can be divided into two broad categories: (1) congenital or (2) acquired deficiency **(Table 1)**. Congenital GHD may be subdivided into central nervous system (CNS) malformations, genetic and idiopathic.

Central Nervous System Malformations
These include midline craniocerebral or mid-facial abnormalities that lead to pituitary defects including pituitary hypoplasia, aplasia and complete absence of the gland. *Anencephaly* is associated with malformed, ectopic or hypoplastic pituitary gland. *Holoprosencephaly* is associated with hypothalamic defects that result in pituitary hormone deficiency. Cleft lip and palate, nasal septal aplasia and a single central incisor are associated with pituitary dysfunction including GHD.

Septo-optic dysplasia (SOD; de Morsier syndrome) This is a congenital malformation of the optic tract that comprises optic nerve hypoplasia and absent septum pellucidum. Approximately 50% of these children have hypopituitarism with the most common hormone deficiency being GH followed by TSH deficiency and ACTH deficiency. These patients are also at risk of developing diabetes insipidus. Patients with this condition have varying degree of visual field defects and diminished acuity and can also present with nystagmus. These patients can also have schizencephaly, absence/hypoplasia of corpus callosum and mental retardation. Mutations in the *HESX1* gene can manifest as SOD. However, in the majority of cases a definitive etiology is lacking. Fetal vascular accidents, young maternal age and maternal use of valproic acid are some of the predisposing factors of the condition. Approximately one-third of patients with optic nerve hypoplasia without involvement of the septum pellucidum are diagnosed with hypopituitarism.

Pituitary stalk interruption (aplasia/hypoplasia) This can occur during birth due to asphyxia with compromise to the vascular supply of the pituitary stalk. Both Diamond–Blackfan and Fanconi anemia are associated with interrupted pituitary stalk and GHD.

Empty sella syndrome This is diagnosed by MRI and is frequently associated with hypopituitarism and isolated GHD. Empty sella is composed of an enlarged pituitary fossa.

Genetic Etiologies

Syndromes These include Pallister–Hall syndrome (hypothalamic hamartomablastoma, micropenis, cryptorchidism), Rieger syndrome which is inherited in an autosomal dominant manner and is due to haploinsufficiency of *PITX2* gene (coloboma, dental hypoplasia, and prominent umbilicus), Prader–Willi syndrome (PWS) resulting from partial deletion of chromosome 15 or maternal uniparental disomy leads to GHD that is thought to be hypothalamic in origin.

Mutation in genes involved in GH production Mutations in the genes involved in development of the pituitary gland, GHRH receptor gene and growth hormone gene can lead to GHD.

1. Mutations in transcription factors responsible for pituitary formation and differentiation:

As described above the development of the pituitary gland is under the control of the coordinated expression of a cadre of transcriptional factors including HESX, LHX3/LHX4, SOX3, PITX2, and GLI2 that are responsible for the development of different pituitary hormone specific cell types. Mutations in these proteins are rare but can be the underlying etiology in patients with pituitary dysfunction where there is no other obvious etiology such as trauma or tumor.

Mutations (mainly homozygous) in *HESX1* gene located on chromosome 3p21.2 results in SOD and hypopituitarism inherited in an autosomal recessive manner.

PTX2 is an early development factor expressed in the rostral brain and is responsible for development of the pituitary gland and mutation in this gene primarily affects gonadotropes and to a lesser extent somatotropes and thyrotropes. This gene has been shown to be mutated in Rieger syndrome.

LHX3 is expressed in the anterior and intermediate lobes of the pituitary gland, the ventral hindbrain and spinal cord. The expression of this gene is responsible for differentiation of pituitary cells into somatotropes, lactotropes, thyrotropes and gonadotropes. Loss of function mutation leads to hypopituitarism with deficiency in GH, TSH, PRL, LH, and FSH. Other syndromic symptoms associated with these patients can include normal, hypoplastic, or enlarged anterior pituitary, a rigid spine with limited neck rotation, hearing loss, and ACTH deficiency.

PROP1 (prophet of Pit-1) is involved in the early determination and differentiation of multiple pituitary cell forms. Mutation in this gene is inherited autosomal recessively and results in deficiency of GH, prolactin, TSH, FSH, LH and occasionally ACTH. It is also a gene required for expression of POU1F1. Defects in POU1F1 (Pit-1) are associated with deficiency in prolactin, TSH and GH producing cells.

2. Mutation in the growth hormone gene (isolated growth hormone deficiency):

Type 1A This is characterized by large deletions in the *GH* gene leading to severe clinical phenotype including severe growth retardation in infancy and dwarfism. These patients frequently develop antibodies against exogenous GH due to lack of immune tolerance as a result of absence of GH in the intrauterine period. These patients eventually require IGF-1 therapy.

Type 1B This is a less severe autosomal recessive form of GHD.

Type II It is the most common form of isolated growth hormone deficiency (IGHD) and is inherited as an autosomal dominant condition.

Type III X-linked inherited form of partial IGHD in which the patients also have hypogammaglobulinemia.

3. GHRH receptor mutation:

Nonsense mutation in exon 3 of the GHRH receptor gene results in the *Dwarfism of Sindh*. The moniker *Dwarfism of Sindh* originates from cases of severe familial dwarfism reported from two villages in the Sindh province of Pakistan that have been proven to be due to mutation in this gene. This condition is inherited in an autosomal recessive manner and is commonly mislabeled as IGHD.

Acquired Forms of Growth Hormone Deficiency

Trauma Head trauma has been shown to damage pituitary stalk and infundibulum leading to anterior and posterior pituitary dysfunction including GHD. Birth trauma such as breech delivery, prolonged forceps delivery and prolonged labor all have been associated with hypopituitarism including GHD.

Central nervous system tumors CNS tumors in particular midline tumors such as germinomas, meningiomas, gliomas and colloid cyst of the third ventricle, and gliomas of the optic nerve are some of the causes of hypothalamic insufficiency. Local extension of craniopharyngioma and Hodgkin disease can also lead to hypothalamic dysfunction and thus GHD.

Infiltration and inflammation of brain and hypothalamus Langerhans cells histiocytosis or sarcoidosis can disrupt the pituitary stalk and lead to hypopituitarism and GHD. Viral and bacterial infections of the brain can result in hypothalamic/pituitary deficiency.

Irradiation of brain Cranial irradiation is associated with hypothalamic/pituitary dysfunction; the degree of pituitary involvement is dependent on the dose of radiation. Low dose irradiation leads to isolated GHD and higher doses lead to multiple pituitary hormone deficiency. A large proportion of children that receive irradiation to head of more than 30 Gy are GH deficient 5 years or more years out from therapy.

GROWTH HORMONE RESISTANCE

Failure to respond to exogenous or endogenous GH with appropriate growth rate and metabolic responses is defined as a GH resistant state. Conditions that result in GHR can be classified as genetic or acquired **(Fig. 3)**. The cardinal feature of all of the conditions described below is a clinical phenotype resembling GHD but the patient has *elevated circulating levels of GH*.

Genetic Etiologies

Conditions involving defects in GH receptor or postreceptor signaling can lead to elevated GH levels with poor growth. Conditions that lead to IGF-1 receptor defect or IGF-1 synthesis will also lead to GHR with poor growth and elevated GH. By definition GH treatment does not elicit a satisfactory response in these patients and treatment with IGF-1 may be the treatment of choice.

Growth Hormone Receptor Gene Mutation

Laron et al. were the first to describe clinical phenotype resembling GHD with high circulating GH level (Laron dwarfism), and this syndrome was subsequently attributed to mutations or deletions in parts of the GH receptor gene coding for the extracellular domain of the GH receptor gene. The human GH receptor gene is located on chromosome 5 and spans 86 kilobase pairs. Approximately 250 patients with Laron syndrome have been reported worldwide of which two-thirds are Arabs, Middle Eastern Jews and Oriental and Ecuadorian and the rest are Mediterranean or South Asian in origin.

Defects in Growth Hormone Receptor Signaling Pathways

STAT 5b mutations Growth hormone binds to its receptor, recruits and phosphorylates STAT 5b which in turn binds to and activates transcription of target genes that results in growth. Mutations

STAT 5b mutation
• Growth failure: severe
• GH: elevated
• GH binding protein: normal
• IGF-1: very low
• IGFBP3: very low

ALS mutation
• Growth failure: none/moderate
• GH: normal
• GH binding protein: normal
• IGF-1: very low
• IGFBP3: very low

***IGF-1 gene* mutation**
• Growth failure: severe
• GH: evevated
• GH binding protein: normal
• IGF-1: absent/high (partial)
  gene deletion/abnormal IGF-1)
• IGFBP3: low/normal

Growth hormone receptor deficiency
Recessive form
• Growth failure: severe
• GH: elevated
• GH binding protein: absent/low
• IGF-1: very low
• IGFBP3: very low
Dominant form
• Growth failure: mild/moderate
• GH: elevated
• GH binding protein: increased
• IGF-1: very low
• IGFBP3: low-normal

IGF-1 receptor mutation
• Growth failure: mild/moderate
• GH: elevated
• GH binding protein: normal
• IGF-1: normal/elevated
• IGFBP3: normal/elevated

Genetic

Growth hormone resistance

Acquired

Renal disease
• Growth failure: mild/severe
• GH: normal
• GH binding protein: decreased
• IGF-1: normal
• IGFBP3: increased

GH inhibiting antibodies
• Growth failure: severe
• GH: absent
• GH binding protein: normal
• IGF-1: very low
• IGFBP3: low

Liver disease
• Growth failure: mild/severe
• GH: normal
• GH binding protein: decreased
• IGF-1: normal
• IGFBP3: increased

Malnutrition
• Growth failure: none/mild
• GH: elevated
• GH binding protein: decreased
• IGF-1: varied
• IGFBP3: varies

Diabetes mellitus
• Growth failure: none/mild
• GH: elevated
• GH binding protein: decreased
• IGF-1: decreased
• IGFBP3: increased

Figure 3 Etiology of growth hormone resistance

(inherited autosomal recessively) in the gene coding for STAT 5b have been reported in approximately 10 patients. These patients apart from having identical phenotype to the GH mutation patients are also prone to immunodeficiency (T cell functional defects).

Conditions that Result in IGF-1 Deficiency due to Either Mutation in the IGF-1 Gene or IGF-1 Receptor Abnormalities or its Bioavailability

Mutation in the IGF-1 gene Mutation in this gene leads to failure of IGF-1 synthesis. These patients have low IGF-1, normal IGFBP3 and elevated GH levels but lack the craniofacial phenotype that is present in severe GHD and GH receptor deficiency.

Mutation in the IGF-1 receptor Homozygous mutation in this receptor is lethal. Heterozygous mutations have been described and lead to severe intrauterine growth retardation. These patients have normal/high IGF-1.

Mutation in the acid labile subunit gene (ALS) Acid labile unit is a protein that regulates the bioavailability of the IGF-1. ALS only binds to IGF-1 and IGFBP3 as part of the ternary complex and not to either one of these proteins individually. Patients with mutation in the *ALS* gene have an undetectable ALS and extremely low IGF-1 and IGFBP3, yet growth impairment is not as severe as that seen in GH deficient patients.

Acquired Growth Hormone Resistance

Growth hormone insensitivity can be caused by chronic illness like malnutrition (Kwashiorkor is characterized by elevated circulating levels of GH with low levels of IGF-1), liver disease

(IGF-1 biosynthesis is affected), poorly controlled diabetes mellitus (insulin deficiency results in decreased hepatic expression of the GH receptor and low IGF-1 production and a concomitant increase in IGFBP1 that inhibits IGF-1 action) and other catabolic states. Circulating antibodies to GH or its receptor can also cause growth failure.

DIFFERENTIAL DIAGNOSIS FOR PATIENTS WITH SHORT STATURE

While investigating a child with short stature suspected to be due to GHD, it is important to consider other etiologies for short stature and investigate for these accordingly.

Endocrinopathies

Hypothyroidism

One of the early and more prominent sign of acquired hypo-thyroidism is poor growth velocity and relative short stature. Hence, obtaining a TSH and free T4 is indicated in a child with poor growth velocity to exclude primary/secondary hypo-thyroidism.

Cushing Syndrome

Excessive glucocorticoids, whether exogenous or endogenous (excess ACTH or primary adrenal tumor), is a potent inhibitor of growth and negatively impacts growth velocity. GH secretion in these patients is typically normal and so is the circulating IGF-1 concentration.

Pseudohypoparathyroidism

These patients have dysmorphic features, poor growth velocity, obesity, and hypocalcemia and hyperphosphatemia due to parathyroid hormone (PTH) resistance.

Rickets

Both vitamin D deficient rickets and hypophosphatemic rickets lead to bony abnormalities like bowed leg resulting in short stature.

Chronic Diseases

Malnutrition

It is the most common cause of growth failure worldwide. In protein energy malnutrition, it has been shown that basal and/or stimulated circulating levels of GH are increased. In generalized malnutrition (marasmus) GH levels may be normal/low and IGF-1 levels are typically reduced.

Malabsorption

Poor growth can precede other clinical symptoms and signs of malabsorptive disorder. Celiac disease (gluten enteropathy) and Crohn disease should be considered in differential of poor growth. IGF-1 levels can be low in these conditions, hence it is important to rule these conditions out while investigating for GHD.

Renal Diseases

These include a variety of conditions that affect renal function and cause growth retardation (uremia, Fanconi syndrome and renal tubular acidosis are some examples). IGF-1 levels are usually normal, but there is increase in serum IGFBPs which could lead to inhibition of IGF-1 action.

Pulmonary Diseases

Cystic fibrosis leads to failure to thrive due to the primary pulmonary disease process and/or pancreatic disease. Chronic asthma in children requiring systemic steroids or high doses of inhaled steroids can lead to poor growth. In general, the decrease in growth velocity in these patients is reversible once the dose of inhaled/oral steroids is reduced; however, the extent of the catch-up growth is variable and generally less than satisfactory.

Chronic Infections

Chronic infestation with intestinal and systemic parasites (schistosomiasis, hookworm and roundworm), tuberculosis and HIV are some of the known causes of poor growth in Southeast Asia.

Hematological Diseases

Thalassemia leads to poor growth rate in children due to not only the chronic anemia but also due to iron overload induced endocrinopathies (hypothyroidism and gonadal failure) from chronic transfusions.

APPROACH TO DIAGNOSIS (FLOW CHART 1)

Growth Hormone Deficiency

Although there is debate about the exact criteria for the laboratory diagnosis of GHD, it is generally accepted that a combination of

Flow chart 1 Who to investigate for growth hormone deficiency?
Investigating a child with poor growth

History
- Birth history
- Past medical/surgical history
- Family history
- Nutrition history
- Social environment

Physical examination: General examination (dysmorphic features, birth marks, cardiac/pulmonary examination, abdominal examination, scoliosis, skeletal deformities)
Upper to lower body segment ratio
Growth chart: Assess growth velocity and percentile for height and weight

↓

Whom to investigate:
- Height below 2 SD of mean/mid-parental target
- Poor height velocity over 1 year

↓

Screening Investigations:
- Screen for chronic diseases:
  - Liver function test, kidney function test, hemoglobin
  - ESR, celiac screen, urinalysis
  - Bone age
- Karyotype (in girls)
- Thyroid function tests
- For growth hormone deficiency/resistance: IGF-1 and IGFBP3

Investigation suggestive of a chronic disease
Investigate accordingly for the disease concerned

Clinical and laboratory data suggestive of abnormal GH-IGF-1 axis
Peak GH level < 7–10 ng/mL on GH stimulation test with 2 different stimulants for GH secretion
- Consider brain MRI with pituitary protocol
- If brain MRI abnormal—treat underlying pathology first and then consider GH therapy
- If brain MRI normal—consider growth hormone therapy

clinical, radiological and auxological assessment together with biochemical investigations of the GH–IGF-1 axis should be used to diagnose the condition. In 2000, the Growth Hormone Research Society published consensus guidelines to assist in diagnosis of GHD.

Clinical Assessment for Growth Hormone Deficiency

Patients with following auxologic profile should be evaluated for GHD after excluding chronic illness/syndrome or other endocrinopathies:

- Severe short stature–height below 3 SD of mean for population
- Height below 2 SD of mean for population and height velocity that is more than 2 SD below the mean for 1 year
- Height 2 SD below midparental target height
- Height velocity more than 2 SD below the mean over 1 year or more than 1.5 SD over 2 years in the absence of short stature.

Evaluation consists of a detailed history including prenatal, postnatal environment and review of auxological data from birth. Family history of stature and age of onset of puberty should be reviewed. History of chronic disease/infection, nutritional status, cranial irradiation and psychological status should be reviewed. Parental heights should be obtained and midparental target height should be calculated.

Neonatal period Since fetal growth is largely GH-independent, newborns with GHD are of normal size. Hypoglycemia and prolonged jaundice with biliary sludging can be present in newborns with GHD, and hypoglycemia is more severe when GHD is present with ACTH deficiency. GHD in isolation or when combined with gonadotropin deficiency, in newborn, can present with micropenis and/or cryptorchidism.

Infancy and Childhood Infants with congenital GHD start to exhibit poor growth velocity by 6–12 months of age. Physiological catch-down growth in babies born larger than that predicted from mid-parental height, generally occurs in the first 2–3 years of life. Growth deceleration that occurs between 2 years and 3 years and the onset of puberty is likely to be pathological. A child exhibiting growth deceleration or whose height is 2 SD below the mean for that population warrants investigation for GHD only after excluding other causes of abnormal growth including endocrinopathies (hypothyroidism and Cushing syndrome), chronic diseases, syndromes (Turner syndrome/Prader–Willi syndrome) and skeletal dysplasia.

Children with GHD can have delayed eruption of dentition. GH is a lipolytic hormone and hence deficiency of GH results in increased body fat. However, a marked increase in BMI is not a feature of GHD. High pitched voice, delayed puberty, and micropenis are other features of GHD. Children with GHD exhibit delayed bone age with normal skeletal proportions. Muscle tone is usually low especially in infants leading to delay in development of gross motor skills. GHD results in poor growth of facial bones manifesting as small facies and underdeveloped nasal bridge. Hair growth is sparse in these patients.

Biochemical Assessment

As stated above a combination of clinical and auxologic together with biochemical data should be used to make the diagnosis of GHD. There is no one single biochemical test that is diagnostic of GHD. Since GH secretion from the pituitary gland is pulsatile, it is generally not useful to measure random levels of GH. Hence, if GHD is suspected, it is best to measure IGF-1 and IGFBP3 as a screening test prior to considering pharmacological stimuli to measure pituitary GH reserves. IGF-1 and IGFBP3 levels that are below 2 SD of reference range based on age and pubertal status suggest abnormality in the GH axis, but normal levels do not always exclude such a diagnosis. IGF-1 levels may be low in malnutrition and chronic liver disease. Pharmacological agents used to stimulate pituitary release of GH reserve include levodopa, clonidine, glucagon, propranolol, arginine and insulin. By themselves, each pharmacological stimulus has low specificity and hence administering sequentially two agents improves the specificity. GH peak level below 7–10 ng/mL is considered as being sub-normal. The precise threshold for categorizing a GH concentration as being low will depend on characteristics of the GH assay.

Radiological Assessment

In any child that presents with neurological signs/symptoms together with short stature or poor growth velocity, brain imaging and MRI with and without gadolinium with appropriate pituitary cuts is the imaging of choice. A child who fails GH provocative test and had the clinical features consistent with GHD warrants a brain MRI to exclude relevant pathology (abnormal pituitary gland/tumor). Bone age is helpful as it is usually delayed in patients with congenital GHD. It may not be delayed in those with acquired deficiency of short duration.

Growth Hormone Resistance

Clinical Assessment

One of the more prominent clinical finding is severe growth failure. Patients also have phenotypic features that resemble severe GHD including sparse hair, prominent forehead, high pitch voice, small face, small hands and feet, and delayed bone age amongst others.

Biochemical Assessment

Patients with GHR share many clinical features with GHD and hence should be screened with laboratory tests to exclude chronic disease. They also have low IGF-1 and IGFBP3 levels. GH binding protein (represents the extracellular domain of the GH receptor) is low in Laron syndrome patients with mutations in the extracellular domain. In patients with IGF-1 receptor defect, IGF-1 levels can be high.

Growth hormone levels are high when measured during GH provocative testing. These patients have increased levels of IGFBP1 and 2. Demonstration of mutation in the *GH* gene/IGF-1 receptor gene can help make a definitive diagnosis in some cases.

MANAGEMENT

Growth Hormone Deficiency

Once the diagnosis of GHD is made treatment with subcutaneously administered recombinant GH is instituted at a dose of 25–50 µg/kg/day with the aim of treatment being to maximize growth and final adult height with avoidance of side effects; within this framework, the dose will need to be adjusted on an individual basis. In patients with significant obesity, it is preferred to use 0.7–1 mg/m^2/day dosing rather than based on body weight. Patients with GHD exhibit a marked increase in growth velocity averaging 10–14 cm in the first year. This effect on growth velocity tends to wane over time.

Monitoring

Child on GH injections should be monitored every 3–4 months to assess how effective the drug is improving height velocity. Although side effects of GH are rare in children, they should be monitored with each visit. These include headaches (assessing for raised intracranial pressure), arthralgia, slipped capital femoral epiphysis, diabetes mellitus, and prepubertal gynecomastia. In epidemiological studies, higher circulating

concentrations of IGF-1 have been linked to certain malignancies in the normal population. Hence, there is a theoretical risk of increased risk of malignancy in patients treated with GH and the goal should be to keep IGF-1 level within normal range for age and pubertal status.

Poor growth in a child with GHD being treated with GH should prompt evaluation of thyroid hormone status since thyroxine deficiency can decrease the effectiveness of GH. Similarly, excessive doses of glucocorticoids in patients with ACTH deficiency as part of multiple pituitary hormone deficiency can dampen GH effectiveness. Hence every effort should be made to keep the glucocorticoid dose to the minimum required for physiological replacement and well-being.

Growth Hormone Resistance

Patients with GHR do not respond to GH. Recombinant IGF-1 was made available for subcutaneous use in 1990. The current recommended starting dose is 80 μg/dose twice daily. Maximal improvement in height is seen in patients with GHR/GH insensitivity within the first year and effect tends to wane in subsequent years.

Monitoring

A child on IGF-1 injection needs to be followed 3–4 monthly to follow growth velocity and monitor for side effects. One of the major side effects of recombinant IGF-1 is hypoglycemia that has been seen in about half the patients treated and is generally managed with food intake around the time of injection. Amongst other side effects that need to be monitored include benign intracranial hypertension, lymphoid hypertrophy (increased snoring and hypoacusis), and an increase in both lean and fat mass leading to increased BMI.

OUTCOME AND PROGNOSIS

We have come a long way since the isolation of pituitary GH in 1956. Prior to the availability of recombinant GH (in use since 1985), there was a concern of acquiring Creutzfeldt-Jakob disease with use of cadaveric GH which was also available only in limited supply. Since advent of recombinant GH, the quality of life of patients with GHD has improved significantly. Patients with IGHD or those associated with multiple pituitary hormone deficiency have a good prognosis for being healthy and maintaining a good quality of life.

Our knowledge regarding GHR is incomplete. Further progress in understanding the various mechanisms underlying this syndrome will help formulate novel treatments for this group of patients.

IN A NUTSHELL

1. Any patient with growth velocity below 2 SD of the mean of the population needs to be screened for GHD/GHR.
2. Accurate auxologic measurement assessment is crucial to making the diagnosis of GHD or GHR.
3. Random GH levels are not helpful in making biochemical diagnosis of GHD. Surrogate markers of GH action, IGF-1 and its primary binding protein IGFBP3, are useful screening tools for GHD.
4. In a child with poor growth being investigated for GHD, it is important to exclude other chronic diseases and endocrinopathies that cause poor growth.

MORE ON THIS TOPIC

Backeljauw PF, Dattani MT, Cohen P, Rosenfeld RG. Disorders of growth hormone/insulin-like growth factor secretion and action. In: Sperling MA. Pediatric Endocrinology. 4th ed. Philadelphia: Elsevier/Saunders; 2014. pp. 291-404.

Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: Summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85(11) 3990-3.

Romero CJ, Dauber A, Cohen LE. Childhood growth hormone deficiency and hypopituitarism. In: Radovick S, Macgillivray MH. Pediatric Endocrinology: A Practical Clinical Guide. 2nd ed. New York: Springer Science; 2013. pp. 3-27.

Rosenbloom AL. Growth hormone insensitivity. In: Radovick S, Macgillivray MH. Pediatric Endocrinology: A Practical Clinical Guide. 2nd ed. New York: Springer Science; 2013. pp. 29-53.

Rosenbloom AL, Connor EL. Hypopituitarism and other disorders of the growth hormone-insulin-like growth factor-1 axis. In: Lifshitz F. Pediatric Endocrinology. 5th ed. New York: Taylor & Francis Inc; 2006. pp. 65-99.

Chapter 44.4
Polyuria, Diabetes Insipidus and Syndrome of Inappropriate Secretion of ADH

Tushar Godbole, PSN Menon

The posterior pituitary is an anatomical extension of the hypothalamus. It contains the axonal processes of the secretory neurons of the supraoptic and paraventricular nuclei of hypothalamus which produce, store and release the two hormones, arginine vasopressin (AVP, also known as antidiuretic hormone, ADH) and oxytocin.

PHYSIOLOGY OF WATER BALANCE

Regardless of large variations in water intake and evaporative water losses, serum osmolality is tightly maintained in a narrow range (280–295 mOsm/kg). This is accomplished by regulating the intake and output of free water. Intake requires the availability of water and an intact thirst mechanism. Excretion is controlled through the kidney via AVP.

Children have larger proportions of body water and have higher liquid intake during the early years of their lives. This poses challenges while treating disorders of water homeostasis in children. The control of plasma osmolality requires a complex integration of endocrine, paracrine, neural and behavioral systems. These include:

The sensors Various nuclei like the preoptic nucleus and organum vasculosum of the lamina terminalis, also called as osmoreceptors, are situated in the anterior hypothalamus and are capable of sensing changes in serum osmolality. They also receive minor inputs from various pressure and volume sensing organs. After stimulation, they send efferent signals to supraoptic and paraventricular nuclei to secrete AVP.

Regulation of water output **(Table 1)** Increase in the serum osmolality to the tune of even 1% above 283 mOsm/kg triggers the secretion of AVP. Once released, it stays in the circulation for 10 minutes. AVP acts on the V2 receptors of the cells of the collecting tubules in the kidneys. This causes expression of aquaporin 2 channels on the luminal membrane and causes absorption of free water; with parallel increase in urine osmolality. The concentration of AVP is directly proportional to the rise in serum osmolality. With maximum effect of AVP, urine osmolality can reach up to 900–1,200 mOsm/kg. Drop in blood volume is also a stimulus, though weaker than osmolality. Pain, stress, nausea and certain drugs also stimulate secretion of AVP **(Fig. 1)**.

Table 1 Common causes of polyuria in children and adolescents

Increased intake	Primary/psychogenic polydipsia (adolescents) Intraoperative fluid excess
Osmotic diuresis	Diabetes mellitus, mannitol
Failed renal reabsorption	Renal tubular acidosis Bartter and Gitelman syndromes Diabetes insipidus: central/nephrogenic
Increased solute excretion	Cerebral salt wasting Primary adrenal failure (mineralocorticoid deficiency) Mineralocorticoid resistance
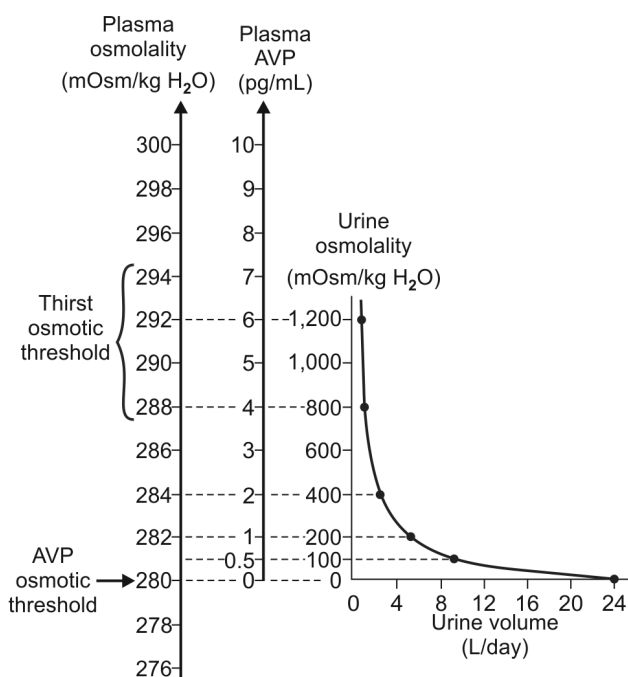
Figure 1 The rise in plasma arginine vasopressin levels and exponential rise in urine osmolality in response to the rise in the plasma osmolality. Note that the threshold for thirst activation is much higher than threshold for AVP release.
Source: Robinson AG. Clinical Endocrinology and Metabolism. 1985; 14:55-88, with permission.

Regulation of intake-thirst mechanisms Rising serum osmolality and, to a lesser extent, hypovolemia trigger thirst. This mechanism, however, is activated after the initiation of AVP secretion. Hence, thirst is the savior when AVP fails to act, or is deficient. If thirst sensation is impaired, it makes the patient vulnerable to severe dehydration and hypernatremia.

Other systems contributing to water homeostasis Renin-angiotensin system responds to volume depletion and exerts the pressor effect on blood vessels. It also stimulates aldosterone production, which causes retention of sodium and thereby water retention. Angiotensin II gives inputs to hypothalamic nuclei. The natriuretic peptides (atrial, brain and C-type) act through inhibition of angiotensin II and aldosterone, thus causing natriuresis. These peptides are activated during conditions of volume overload.

APPROACH TO A CASE OF POLYURIA

In children polyuria is defined as urine output more than 4 mL/kg/hour or 2 L/m^2/day. Sometimes a urinary tract infection may appear to be polyuria due to the increased frequency of micturition. It is important to actually document the urine output to confirm polyuria before going ahead with the panel of biochemical and hormone testing. However, this is difficult in infants and toddlers, especially girls. In such cases, weighing the diapers helps. Associated polydipsia and disturbed night sleep due to thirst/urine frequency are reliable indicators of significant polyuria. The common causes of polyuria in children are listed in **Table 1**. History of central nervous system (CNS) insult such as head injury, meningitis or history of CNS symptoms such as headaches and visual disturbances needs to be asked in detail. Deficiency of other pituitary hormones needs to be looked for, such as short stature, central hypothyroidism, delayed puberty and easy fatigability with weight loss. Estimation of blood sugar, serum electrolytes, blood urea nitrogen (BUN), creatinine, urine

osmolality and specific gravity, urinary glucose, urine calcium and blood gases will rule out other causes of polyuria such as diabetes mellitus, hypercalciuria and renal tubular acidosis. Persistent polyuria in a diabetic child even after a good sugar control should raise suspicion of Wolfram (DIDMOAD) syndrome.

DIABETES INSIPIDUS

The term diabetes insipidus (DI) means passing large quantities of tasteless (dilute) urine. It reflects the inability of the kidneys to reabsorb the free water. It may result from deficiency of AVP secretion or its action **(Table 2)**. Nephrogenic DI is dealt with in detail in Section 41.

Clinical Features

A child with DI usually presaents with polyuria with preference to cold water as the main complaint. With intact thirst, the dehydration is compensated and the sodium as well as plasma osmolality are kept normal. Hypernatremia can be seen during infancy, during additional fluid losses such as diarrhea, or when the access to water is limited, e.g., post-CNS surgery. Midline defects and nystagmus are the clues toward septo-optic dysplasia. In cases of panhypopituitarism, the DI may get evident only after replacement of glucocorticoids. The presentation of DI during infancy is with growth failure, fever due to hypernatremic dehydration, and hydronephrosis.

Investigations

The osmolality of the serum is mainly contributed by sodium, urea and glucose. It can be calculated by the following formula:

Serum osmolality = 2[Na$^+$] + [Glucose/18] + [BUN/2.8] mOsm/kg

where Na is measured in mmol/L and both glucose and BUN in mg/dL. However, the correct and more reliable method is to actually measure the osmolality by an osmometer using the depression of freezing point method.

It is important to establish the diagnosis and then differentiate between central versus nephrogenic DI. Passing of hypo-osmolar urine [< 300 mOsm/kg] in the presence of hypernatremia or high serum osmolality (> 300 mOsm/kg) clinches the diagnosis of DI and one can proceed with testing for response to AVP. This is likely to be picked up when the urine and blood are collected soon after waking up before taking any fluids. But most of the patients have to drink frequently in the night, compensating for the dehydration and hypernatremia. In such cases, a formal water deprivation testing is required to induce hyperosmolality and make the diagnosis **(Flow chart 1)**.

Water Deprivation Testing
The following are the prerequisites before attempting this test:
- Child is not on any drugs for polyuria
- Normal or corrected cortisol and thyroid axis
- Child should be hospitalized and consent taken
- A good lab support to provide urgent osmolality readings.

During the testing, the child is deprived of water to cause dehydration up to 5% of baseline weight or till serum osmolality goes above 300 mOsm/kg. This may take between 6 hours and 12 hours depending on the severity of polyuria. Serial recordings of weight, blood pressure and urine output are taken along with samples for urine and serum osmolality. If urine osmolality rises above 750–800 mOsm/kg, it rules out DI and suggests excess drinking. Inability to concentrate urine above 300 mOsm/kg when serum osmolality has reached 300 mOsm/kg and above, gives the diagnosis of DI. Urine values in-between suggest a partial DI or long standing primary polydipsia. Plasma AVP estimation is generally not required, but can be done in doubtful cases or in infants where formal testing is not possible. Measurement of the copeptin (C-terminal of the AVP prohormone) may serve as the surrogate marker of endogenous AVP secretion, but it is not yet validated.

The next step is to demonstrate the response to AVP while continuing with water deprivation. A serial rise above 50% in urine osmolality after a subcutaneous dose of AVP, 5 IU/m^2 confirms central DI, while a failed response suggests nephrogenic DI.

Imaging of the pituitary The normal posterior pituitary bright spot is usually absent in central DI, but it is not a specific sign. Thickening of the pituitary stalk may be seen with infiltrative or inflammatory conditions.

Table 2 Etiology and classification of diabetes insipidus

Central		
Congenital	*Panhypopituitarism*: Septo-optic dysplasia Holoprosencephaly Familial DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness)	
Acquired	*Infection*: Tuberculous meningitis, others *Trauma*: Stock transection *Vascular insult*: Hypoxic injury, infarction, Sheehan's syndrome (postpartum) *Tumor*: Craniopharyngioma, optic glioma, germinoma, adenoma with apoplexy *Infiltration*: Histiocytosis X, autoimmune, sarcoidosis, leukemia	
Drugs	Phenytoin, halothane and alcohol	
Idiopathic	Up to 10–50% of cases	
Nephrogenic		
Congenital	X-linked, autosomal dominant, autosomal recessive	
Acquired	*Metabolic*: Hypocalcemia, hypokalemia *Renal disease*: Polycystic kidney, sickle nephropathy, obstructive uropathy, acute tubular necrosis, chronic pyelonephritis	
Drugs	Amphotericin B, demeclocycline, lithium, rifampin	

Flow chart 1 Approach to the differential diagnosis of diabetes insipidus
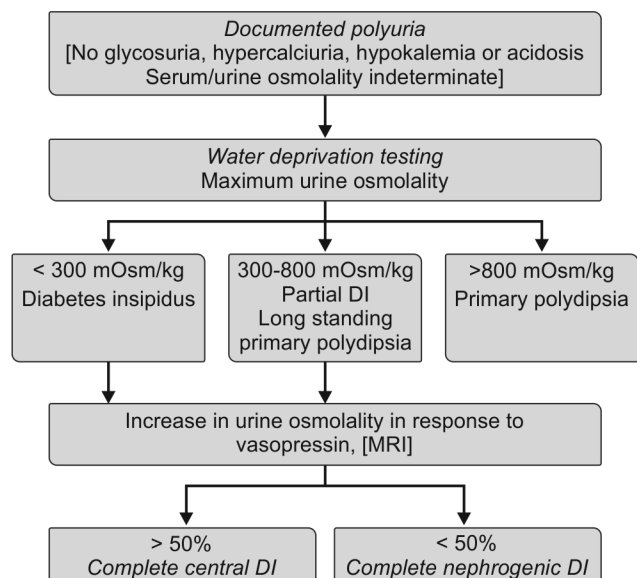
Management

Post-CNS Surgery/Trauma

Excess of intraoperative intravenous fluids is a common cause of polyuria during initial postoperative hours. Polyuria during first 24 hours of trauma or surgery may be transient DI and may revert spontaneously or develop into syndrome of inappropriate secretion of ADH (SIADH). In an unconscious patient, it is important to maintain balanced input and monitor serum sodium. In a conscious patient with intact thirst, ad-libitum water intake should be allowed. In case of massive polyuria, subcutaneous vasopressin may be given with a frequency just enough to control polyuria. Long acting desmopressin (DDAVP) is generally avoided, as the polyuria may be transient and DDVAP may cause hyponatremia.

Triple Response Following Head Injury

Following head injury or brain surgery, there is stunning of the neurons with surrounding edema leading to transient AVP deficiency and transient DI. As the edema subsides, beyond 2 days, there is release of AVP from the dying neurons giving rise to SIADH. After 10–14 days, permanent DI again reappears.

Permanent Diabetes Insipidus

After confirming the diagnosis, underlying cause if any, should be treated. DDAVP (a synthetic analog of AVP) has a half-life of 8–24 hours and is suitable for once or twice daily dosing. It is available as tablets and intranasal spray. Intranasal spray can be given at bedtime with dose between 2.5 µg and 10 µg. Commercial preparations deliver 10 µg as a spray, which may be a high dose for infants, hence a smaller dose can be sprayed intranasally using an insulin syringe. Oral tablets are also effective but the dosing is highly variable between 100 mg/day and 1,000 mg/day. It is advised to allow washoff of the drug (marked by reappearance of polyuria) before the next dose, in order to prevent hyponatremia. Free access to water during summer and illness is a must.

Nephrogenic Diabetes Insipidus

This clinical entity is discussed in detail in Section 41.

SYNDROME OF INAPPROPRIATE SECRETION OF ADH

Syndrome of inappropriate ADH secretion is also called as syndrome of inappropriate antidiuresis. This is caused by excess AVP secretion or inappropriate activation of its receptors in the kidneys. This causes fluid retention, dilutional hyponatremia, and low urine output with inappropriately high osmolality. Most of the volume excess is intravascular, hence there is no frank edema or anasarca. In chronic SIADH (beyond 48 hours), there is euvolemia due to compensatory mechanisms such as natriuresis and intracellular solute depletion.

The common causes of SIADH are given in **Table 3**.

Clinical Features

Worsening of neurological status in a setting of CNS injury may be due to SIADH-induced hyponatremia. Lethargy, confusion, altered sensorium are the symptoms of acute hyponatremia. Severe cases may develop seizures and unconsciousness. Chronic cases manifest with nausea, headaches, vomiting and muscle cramps. As opposed to other causes of hyponatremia such as cerebral salt wasting (CSW), in SIADH the child is not volume depleted. There are no features of dehydration, weak pulses or tachycardia.

Investigations

Serum osmolality is low (< 275 mOsm/kg). Serum uric acid is low in SIADH, reflecting the increased intravascular volume. Urine

Table 3 Etiology of syndrome of inappropriate secretion of ADH

Neurological/ Psychiatric	Trauma, post-CNS surgery *Infection*: Meningitis, encephalitis, abscess *Vascular*: Infarct, sinus thrombosis, bleeds Neoplasms Postictal phase of generalized seizure Guillain-Barré syndrome
Drugs	*Anticancer*: Vincristine, cyclophosphamide *Psychiatric drugs*: Amitriptyline, haloperidol Carbamazepine DDAVP overtreatment/misuse
Pulmonary	Pneumonia Lung abscess ARDS Positive pressure ventilation
Ectopic AVP	Carcinoma of lung, bronchus, pancreas, intestine and thymus Lymphoma, leukemia
Nephrogenic	Activating mutations of V2 receptors [Nephrogenic SIADH]
Miscellaneous	AIDS

Abbreviations: ARDS, acute respiratory distress syndrome; AVP, arginine vasopressin; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

osmolality is above 100 mOsm/kg (inappropriately high for hypo-osmolar plasma). The urinary sodium content is also marginally elevated (> 30 mEq/L) due to suppressed aldosterone and excess of atrial natriuretic peptide (ANP). A low urinary sodium (< 30 mEq/L) with elevated serum BUN suggests hypovolemia as the cause for hyponatremia, and rules out SIADH.

Management

Treatment is aimed toward restoring the sodium and water balance, and treating the underlying cause. Treating the underlying lung disorder or weaning from positive pressure ventilation promptly resolves the hyponatremia. Asymptomatic hyponatremia is corrected by limiting fluid intake, thereby causing loss of total body fluid. This can be achieved by giving fluids equal to insensible water loss plus the urine output. Hyponatremia should be corrected at a rate not more than 12 mEq in a day. Rapid correction may result in central pontine myelinolysis. Severe hyponatremia may be treated with furosemide-induced diuresis, which causes more water loss as compared to sodium. The urine output is then replaced with 3% saline. If the fluid restriction limits the food intake (as in infants), a situation similar to nephrogenic DI may be created with the help of demeclocycline. Newer V2 receptor antagonists like tolvaptan are being tried in adult patients with SIADH and hyponatremia. Vaptans prevent free water absorption from V2 receptor-mediated aquaporin channels.

CEREBRAL SALT WASTING

As the name suggests, this disorder is due to excess secretion of natriuretic peptides as a result of CNS injury, giving rise to natriuresis. The excess ANP suppresses AVP and aldosterone, causing polyuria and salt wasting. Clinical features include dehydration, hypovolemia and symptoms of hyponatremia. Lab tests reveal low serum sodium and elevated urinary sodium (> 150 mEq/L). Both SIADH and CSW have hyponatremia and increased urinary sodium, but the degree is severe in CSW with hypovolemia. Both DI and CSW have polyuria and dehydration but hyponatremia is seen only in CSW.

Cerebral salt wasting usually resolves spontaneously in 2–4 weeks after the CNS injury. Till that time, it is managed by

replacing the losses with isotonic (0.9%) saline and oral salt. Slow correction of serum sodium is recommended to prevent pontine myelinolysis.

PRIMARY POLYDIPSIA

It is the primary increased intake of water that gives rise to polyuria in these cases. The renal concentrating mechanisms are normal and the water deprivation testing usually yields increasing urine osmolality after deprivation. However, in severe long-standing cases, due to loss of medullary gradient, there may be partial concentration. It may be seen in psychiatric cases with compulsive water drinking (psychogenic), or in cases with altered thirst mechanisms (dipsogenic). The set-point of the thirst center can get altered after neurosurgical procedures like surgery for craniopharyngioma. Treatment involves restriction of water intake to physiologic levels. Drug therapy has no proven role.

MORE ON THIS TOPIC

Fenske W, Allolio B. Clinical review: Current state and future perspectives in the diagnosis of diabetes insipidus: a clinical review. J Clin Endocrinol Metab. 2012;97:3426-37.

Muglia IJ, Majoub JA. Disorders of Posterior Pituitary. In: Sperling MA. Pediatric Endocrinology. 3rd ed. Philadelphia: Saunders; 2008. pp. 195-227.
Ranadive SA, Rosenthal SM. Pediatric disorders of water balance. Endocrinol Metab Clin North Am. 2009;38:663-72.
Verbalis JG. Disorders of body water homeostasis. Best Pract Res Clin Endocrinol Metab. 2003;17:471-503.

IN A NUTSHELL

1. Water and sodium are controlled in a precise way, with complex interplay of various mechanisms.
2. Primary polydipsia, DI and CSW present with polyuria. While serum and urine sodium helps in differentiating between DI and CSW, differentiating between polydipsia and DI may require formal water deprivation testing.
3. Syndrome of inappropriate secretion of ADH and CSW both have hyponatremia with elevated urinary sodium, but CSW is accompanied by hypovolemia. SIADH needs fluid restriction, while CSW needs fluid and salt replacement.
4. Slow correction of the altered sodium levels is important for preventing CNS damage. Achieving euvolemia and eunatremia is the goal, but the underlying cause needs to be evaluated and corrected if possible.

Chapter 44.5
Thyroid Hormone Physiology
Anna Simon

The thyroid gland is the first endocrine gland to develop in the human body. This development and maturation can be considered in two phases; the first phase of embryogenesis of the thyroid gland and the second phase of maturation of the hypothalamic-pituitary-thyroid axis including hormone secretion and regulation. Thyroxine (T4) and triiodothyronine (T3), the two active hormones secreted from the thyroid gland, bring about their actions via a nuclear receptor, regulating the production of a variety of enzymes and proteins **(Table 1)**.

DEVELOPMENT OF THE THYROID GLAND

The thyroid gland originates as an outpouch from the floor of the primitive pharynx at the base of the tongue near the foramen cecum and descends through the tissues of the neck to the thyroid bed. The majority of the follicular cells are derived from this outpouching. This structure is further laterally fused with derivatives from the fourth branchial arches, the cells of which develop into the C cells or the parafollicular cells. As the thyroid gland descends, it remains connected to the foramen cecum by the thyroglossal duct which later becomes obliterated by the 7–10 gestational week. Failure of subsequent obliteration of the thyroglossal duct results in thyroglossal cyst formation.

A panel of transcription factors have now been identified, e.g., TTF1, NKX2.1, NKX2.5, PAX 8, FOXE1, HHEX are involved in organogenesis, development, differentiation and migration of thyroid gland.

Functional Maturation of the Thyroid Gland in the Fetus

Thyroglobulin synthesis has been documented as early as 4 weeks of gestation and iodide trapping by 8–10 weeks. The capacity to concentrate iodide and secrete thyroxine (T4) is acquired by 12 weeks of gestation. The maturation of the hypothalamic-pituitary-thyroid axis occurs in the second half of gestation, but complete maturation of the normal feedback mechanisms occur only during the second postnatal month.

Regulation of the Hypothalamic-Pituitary-Thyroid Axis

Thyroid stimulating hormone (thyrotropin, TSH) secreted from the pituitary thyrotropes binds to the TSH receptors (TSHR) and mediates several effects on thyroglobulin synthesis, thyroid hormone synthesis and release and also on thyroid cell growth. TSH secretion is regulated by thyrotropin-releasing hormone (TRH) production from the hypothalamus. Both triiodothyronine (T3) and T4 exert a negative feedback effect on TRH and TSH secretion.

Formation and Secretion of Thyroid Hormones

Thyroglobulin is synthesized by the thyroid follicular cells and is found in high concentrations in the colloid. Iodide is taken up at the basal membrane of the follicular cells by a sodium-iodide symporter and is transported to the cell-colloid interface where thyroid hormone synthesis takes place. The process is initiated by iodide transporter protein complex (which includes pendrin), thyroid peroxidase (TPO) and thyroid oxidases (DUOX1, DUOX2). The production of hydrogen peroxide by thyroid oxidase is the rate limiting step in thyroid hormone synthesis. TPO catalyzes the oxidation to iodine in the presence of peroxide and further catalyzes the iodination of tyrosine residues within the thyroglobulin molecule (organification) to form monoiodotyrosine and diiodotyrosine which couple together to form T3, T4 and reverse T3 (rT3) which are released into the blood stream. The released mono and diiodotyrosines are deiodinated and the iodine content is recycled for further use.

The thyroid secretes T4 (80%) and T3 (20%) and these hormones are carried in the blood stream bound to thyroid-binding globulin (TBG), transthyretin (TTR) and albumin. The actions of thyroid hormones are given in **Table 1**.

THYROID FUNCTION IN NEONATES

Thyroid Function in the Term Neonate

With exposure to cold and clamping of the umbilical cord, the serum TSH rises abruptly to 60–80 mU/L within 30–60 minutes of birth. This physiological surge of TSH then declines rapidly to about 20 mU/L at 24 hours and then gradually to about 6–10 mU/L at 1 week of age. Serum total and free T4 rises in parallel to the TSH surge and peaks at 24–36 hours. The hormonal levels then gradually fall in the first 4 weeks of life and stabilizes at slightly higher values than adults (Total T4 7–16 µg/dL, free T4 0.8–2 ng/dL, TSH 0.5–6 mU/L).

Table 1 Actions of thyroid hormones

CNS development and function	Increases myelin formation
	Stimulation of neuronal cell maturation and migration
	Stimulates dendritic branching and synaptic formation
	Influences other neurotransmitters, enzymes and cell proteins
Growth and development	Direct effects on growth
	Stimulates pituitary GH synthesis and secretion
	Stimulates insulin-like growth factor (IGF) synthesis and action
	Increases protein synthesis and facilitates muscle growth
	Enhances IGF-1 action on the bone/cartilage
Metabolic effects	Increases basal metabolic rate
	Thermogenesis
	Increases gluconeogenesis, glycogenolysis and stimulates insulin-mediated glucose uptake
	Increases lipolysis and fatty acid oxidation
	Stimulation of adrenergic receptor binding

Thyroid Function in the Preterm

Cord serum total T4 and free T4 varies with gestational age. The reference range for thyroid hormones, therefore, is dependent on gestation age and postnatal age. Preterm infants also undergo changes in serum TSH, T4 and T3 similar to term newborns but these changes are smaller because of immaturity of hypothalamic-pituitary-thyroid (HPT) axis. The decline in T4 levels after birth is more profound, resulting in *hypothyroxinemia of prematurity* most marked in infants born prior to 30 weeks gestation. Preterm infants also have very low levels of T3 due to immaturity of hepatic deiodinase. The immaturity of the HPT axis can also result in *delayed rise of TSH* in preterm hypothyroid baby, thereby affecting screening results.

Role of the Placenta

Placental transfer of T4 takes place throughout gestation, permitting relative protection of brain development in the hypothyroid infant, provided the mother is euthyroid. Though the placenta normally has limited permeability to T4, when there is fetal hypothyroidism and a significant gradient between the maternal and fetal circulation, there is an increased transfer of maternal T4 to the fetus. This transplacental transfer of maternal T4 has a critical role in limiting the negative consequences of hypothyroidism in the fetus. In contrast to T4, the placenta is freely permeable to iodide, antithyroid drugs, TSHR antibodies and some IgG immunoglobulins. Thyroglobulin and maternal TSH do not cross the placenta.

Thyroid Functions in the Critically Ill Neonate and Child

Euthyroid sick syndrome or nonthyroidal illness syndrome (NTIS) describes changes in thyroid hormone levels induced by critical nonthyroidal diseases. There are significant changes in the hypothalamic-pituitary-thyroid axis and the syndrome is characterized by low TSH, low T3 and low T4. NTIS has been considered as an adaptive phenomenon, but the cause and effect is still not clear and treatment with thyroxine may not be beneficial. It must also be remembered that drugs like glucocorticoids and dopamine which is often used in sick children can affect thyroid hormone assays.

IN A NUTSHELL

1. The thyroid secretes T4 (80%) and T3 (20%) and these hormones are carried in the blood stream bound to TBG, TTR and albumin.
2. Thyroid stimulating hormone secreted from the pituitary mediates several effects on thyroglobulin synthesis, thyroid hormone synthesis and release and also on thyroid cell growth.
3. Thyroid stimulating hormone secretion is regulated by TRH production from the hypothalamus.
4. Both triiodothyronine (T3) and T4 exert a negative feedback effect on TRH and TSH secretion.
5. At birth, the serum TSH rises abruptly to 60–80 mU/L within 30–60 minutes. This physiological surge of TSH then declines rapidly to about 20 mU/L at 24 hours and then gradually to about 6–10 mU/L at 1 week of age.

MORE ON THIS TOPIC

Fisher DA, Brown RS. Thyroid physiology in the perinatal period and during childhood. In: Braverman LE, Utiger RD. The Thyroid. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 959.

Fisher AD, Grueters A. Disorders of the Thyroid in the Newborn and Infant. In: Sperling MA. Pediatric Endocrinology. USA: Elsevier Health Sciences; 2008. pp. 198-226.

Kratzsch J, Pulzer F. Thyroid gland development and defects. Best Pract Res Clin Endocrinol Metab. 2008;22:57-75.

Chapter 44.6
Hypothyroidism and Thyroiditis
Palany Raghupathy

Hypothyroidism is the most common endocrine disorder in pediatric practice. Untreated congenital hypothyroidism (CH) in early infancy results in profound growth failure with irreversible developmental delay. Untreated hypothyroidism in older children also leads to growth failure, impaired memory and deceleration of metabolic functions. Prompt recognition of the hypothyroid state (by newborn screening in the case of a newborn and clinical evaluation in the older child), initiation of treatment, and continuous regular therapy as well as follow-up will ensure normal physical growth, and motor and intellectual development.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism is the most common and easily preventable cause of mental retardation in children. All efforts should, therefore, be made for timely identification of the affected newborn.

Epidemiology

The incidence of CH in the developed nations is nearly 1 in 2,000–4,000 live births, while studies in India have shown a higher incidence of approximately 1 in 1,200 live births. Newborn screening was established in Quebec, Canada in the 1970s, to diagnose CH early in the newborn period and to avoid the devastating outcome of severe mental retardation in children who were diagnosed late in infancy. Treatment for the affected infants commenced prior to 2 weeks of life and continued regularly will ensure normal physical and mental development **(Fig. 1)**. Newborn screening for CH is now universal in several countries of the world and is clearly warranted as it is a cost effective program for any nation or society.

Figure 1 A tale of two siblings. The younger one (left) with normal growth and development was detected to have congenital hypothyroidism by neonatal screening and was treated regularly. The older child (right) first presented at 2 years 6 months of age, and is not normal yet, physically and developmentally, despite regular treatment begun late

Pathogenesis and Pathophysiology

The causes of CH are listed in **Table 1**. Congenital malformations of the developing fetal thyroid gland or dysgenesis (including agenesis, hypoplasia or ectopia) form the majority of cases (85%). It occurs more frequently in females with a female: male ratio of 2:1. It may be associated with other congenital anomalies in a few cases (5%). Mutations in the *PAX8* gene and some mutations in the *TSHR* gene prevent or disrupt the normal development of the thyroid gland before birth and can cause agenesis or ectopia. Ectopic gland results from an impeded migration of the fetal thyroid from the pharynx to the neck **(Figs 2 to 4)**. The ectopic gland though functional, is incapable of adequate and sustained thyroxine production for life.

Dyshormonogenesis due to defects of iodide transport, peroxidase deficiency causing defective iodine oxidation and organification, or abnormal thyroglobulin (TG) synthesis, inherited by autosomal recessive mode, accounts for the remaining etiology of congenital primary hypothyroidism. Mutations in the *DUOX2, SLC5A5, TG, TPO*, and *TSHB* genes prevent or reduce the production of thyroid hormones, even though the thyroid gland is present.

The other less frequent causes of CH are: secondary or tertiary hypothyroidism, iodine deficiency, maternal thyroid antibodies suppressing neonatal thyroid function. A rare but serious cause is giant hemangioma, often seen in the liver. Increased consumption

Table 1 Causes of congenital hypothyroidism

Permanent	Transient
Dysgenesis	*Drug induced*
Hemiagenesis of thyroid	Antithyroid drugs
Agenesis of thyroid	Iodine
Hypoplastic thyroid	*Iodine deficiency*
Ectopic thyroid	
Dyshormonogenesis	*Maternal antibody induced*
Organification defect	
Iodide trapping defect	
TSH unresponsiveness	
Defective thyroglobulin synthesis	
Iodotyrosine deiodinase deficiency	
Central hypothyroidism	
Panhypopituitarism	
Hypothalamic-pituitary anomalies	
Isolated TSH deficiency	

Abbreviation: TSH, thyroid stimulating hormone.

Figure 2 Ectopic thyroid

Figure 3 Ectopic thyroid: moving higher with deglutition

Figure 4 Lingual thyroid

Table 2 Clinical findings in congenital hypothyroidism in the newborn

Postmaturity, large for date	Rough, dry skin
Hypotonia	Prolonged physiological jaundice
Constipation	
Pallor	**Associated congenital anomalies:**
Hypothermia	Congenital heart disease
Hoarse cry	Chromosomal abnormalities
Feeding/sucking difficulty	Microcephaly
Large tongue	Clubfoot
Umbilical hernia	Subluxation of the hip
Wide fontanels	

Figure 5 Dyshormonogenetic goiter in the newborn

hypothyroidism in the infant. If the mother is also hypothyroid, the infant may have severe hypothyroidism at birth as the placental transfer of thyroxine is minimal in this situation.

Laboratory Tests

Thyroid hormone values in the newborn period are different from those in older age groups as shown in **Table 3**. Hence, thyroid function tests should be interpreted specifically for the age of the child and should include either serum free T4 or total T4 and TSH. It is also important to get thyroid function tests carried out only from reliable and accredited laboratories. T3 estimation is not useful as it may often be normal in CH. Low serum total or free T4

of free T4 occurs due to increased type 3′ deiodinase activity within the hemangioma, converting T4 to reverse T3 and T3–T2. T2 and reverse T3 are inactive thyroid hormones and hence the child develops clinical and biochemical features of primary hypothyroidism and requires thyroxine replacement often in very large doses, until the hemangioma shrinks spontaneously or with treatment. Periodic thyroid function testing is necessary in infants born with a large hemangioma.

Clinical Features

The clinical features of CH are enumerated in **Table 2**. When functional, an ectopic thyroid may escape detection on neonatal screening and may even support normal physical growth and development for a few years. Later, when it fails to deliver quantities of thyroxine commensurate for active growth, the child will present with an ectopically placed enlarged thyroid swelling in the lingual region or in the neck. In the neck, it is often confused for the thyroglossal cyst. Dyshormonogenesis is usually seen with a goiter or easily palpable thyroid gland in the newborn **(Fig. 5)**. When partly functional, it may support normal growth and development in childhood and may present with a goiter for the first time during rapid growth in adolescence.

Transient hypothyroidism caused by maternal factors is listed in **Table 1**. Iodine deficiency in the mother may lead to transient

Table 3 Age-related normal thyroid hormonal values

	TSH (ICMA)* mU/L	T4 (RIA)* μg/dL
Preterm (28–36 weeks of gestation)		
First week of life	0.7–27.0	4.0–17.4
Cord blood (≥ 37 weeks gestation)	2.3–13.2	5.9–15.0
Birth: 4 days**	1.0–38.9	14.0–28.4
2–20 weeks	1.7–9.1	8.1–15.7
21 weeks to 20 years	0.7–6.4	5.6–14.9

* ICMA, immunochemiluminescence assay; RIA, radioimmunoassay.
** Newborn physiological TSH surge occurs half an hour after birth and lasts about 2–4 days

concentrations with markedly elevated serum TSH level are seen in nearly all cases of CH except central hypothyroidism, wherein low serum total or free T4 are seen along with low serum or normal TSH as well. This will need to be distinguished from thyroxine binding globulin (TBG) deficiency.

Radiograph of both knees will show absence of (or small size) of the lower femoral and/or upper tibial epiphyses.

Thyroid nuclear imaging is useful to decipher the etiology of CH and helps in convincing the parents regarding the permanent nature of the condition and the need for lifelong therapy. Nuclear scan must be planned prior to or within a week after commencement of thyroxine to avoid blocking of the radionuclide tracer uptake by the thyroid. ^{99m}Tc scan provides anatomical details of the thyroid. ^{123}I scan with perchlorate discharge test will help to delineate dyshormonogenetic defect of iodide organification.

When nuclear scan is not available readily, therapy with thyroxine should never be delayed. Determination of the etiology in such cases or in doubtful cases may be carried out after the third birthday, after stopping thyroxine safely for 4–6 weeks.

Thyroid ultrasonography is useful to delineate the presence of the thyroid when it is not demonstrated on nuclear scan because of poor tracer uptake caused by maternal thyroid antibodies, or antithyroid drug therapy.

Treatment

Treatment for CH is replacement of the deficient thyroxine in the form of levothyroxine tablet, at a dose of 10–15 μg/kg/day (for newborns), once daily. The tablet is crushed and mixed with a small quantity of water or expressed breast milk and administered with a spoon or dropper ensuring all the particles are given entirely, preferably on an empty stomach. Thyroxine is unstable in suspension form. The parents have to be educated appropriately regarding regular therapy, and the need for its lifelong duration. Dosage adjustment will be required during follow-up with increasing age repeat thyroid function testing is done a month after commencing therapy and subsequently once in 3–6 months. Monitoring of the child's growth and development at regular intervals is essential.

Ectopic thyroid should never be removed, as this may be the only thyroid tissue in the child. Medical therapy with thyroxine replacement will effectively reduce the size of the swollen ectopic thyroid. Even transient hypothyroidism may be potentially harmful to the infant and hence thyroxine therapy should be given temporarily until one is convinced that the infant is able to produce normal amounts of thyroxine required or until resolution of the underlying cause.

If thyroxine therapy had been commenced on purely suspicious grounds without confirming a permanent cause or without adequate etiological work-up initially, thyroxine may be stopped for 4–6 weeks after the age of 3 years to establish the permanent nature of hypothyroidism and thyroid function tests repeated.

Prognosis

Early initiation of thyroxine therapy for permanent hypothyroidism will lead to acquisition of normal academic skills and these children will compare well with their unaffected peers.

HYPOTHYROIDISM BEYOND THE NEONATAL PERIOD

Childhood hypothyroidism with onset after 6 months of age is also known as *acquired hypothyroidism* and may be primary (at the level of thyroid gland), secondary (at pituitary level) or tertiary (at level of hypothalamus).

Epidemiology

Acquired hypothyroidism is sporadic in a large majority of cases. Around 15% of cases are due to inherited biosynthetic defects of thyroxine **(Box 1)**.

Chronic lymphocytic thyroiditis (CLT) or Hashimoto thyroiditis is the most frequent cause of acquired hypothyroidism in 1–2% of adolescents in early to midpuberty, but may also occur in younger children and in either sex with female sex predominating (F : M ratio 2 : 1) in all age groups. This is an autoimmune disease with inherited predisposition and may also be initiated by environmental factors. Activation of CD4 (helper) T-lymphocytes specific for thyroid antigens initiates the autoimmune process. The net result is hypothyroidism due to destruction of the thyroid by lymphocytes and cytokines. However, thyroid stimulation by antibodies may also lead to Graves' disease. Antithyroglobulin and antimicrosomal (antithyroid peroxidase, TPO) antibodies are present in nearly 90% of cases, the latter being more sensitive and specific. Thyroid antibodies serve as useful markers of CLT and are not believed to play a role in the pathogenesis of CLT. Family history of either CLT or Graves' disease is encountered in nearly one-third of cases.

Chronic lymphocytic thyroiditis may present by itself or along with other autoimmune conditions **(Box 2)**, e.g., in 20% of children

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BOX 1 Causes of acquired hypothyroidism in children

Primary hypothyroidism
- Chronic lymphocytic (Hashimoto) thyroiditis
- Chromosomal and other disorders associated with autoimmune thyroiditis **(Box 2)**
- Late onset CH
  – Thyroid dysgenesis
  – Thyroid dyshormonogenesis (inborn errors of thyroid metabolism)
- Drugs
  – Anticonvulsants
  – Amiodarone
  – Lithium
  – Antithyroid drugs
- Infection
- Infiltration
- Iodine deficiency

Secondary/tertiary hypothyroidism
- Craniopharyngioma
- Tumors compressing hypothalamus/pituitary
- Neurosurgery
- Cranial irradiation
- Head trauma

Thyroid hormone resistance.

Abbreviation: CH, congenital hypothyroidism.

BOX 2 Conditions associated with autoimmune thyroid disease

- Down syndrome
- Turner syndrome
- Noonan syndrome
- Klinefelter syndrome
- Addison disease
- Celiac disease
- Polyglandular autoimmune disorder
- Vitiligo
- Alopecia
- Any autoimmune condition.

with type 1 diabetes mellitus or 5% of cases of autoimmune polyglandular syndrome with or without Addison disease. Children with Down, Turner, Noonan and Klinefelter syndromes, juvenile idiopathic arthritis, and systemic lupus erythematosus tend to have a predisposition to develop CLT.

The other causes of childhood hypothyroidism **(Box 1)** are congenital in origin but presenting later in childhood, noted especially with rapid growth during puberty, as in thyroid dyshormonogenesis with a goiter, or ectopic thyroid. Iodine deficiency during pregnancy can lead to simultaneous maternal and fetal hypothyroidism, resulting in irreversible mental retardation (so called endemic cretinism). This was a major public health problem in India, but with mandatory iodization of salt, is fortunately less often encountered now.

Pathogenesis

In CLT, diffuse lymphocytic infiltration occurs with fibrosis, parenchymal atrophy, and eosinophilic changes in acinar cells. Iodine storage becomes defective and synthesis of thyroxine is poor. Two forms of CLT are recognized, viz. goitrous and atrophic. Goitrous form is more common with diffusely enlarged thyroid caused by elevated serum TSH or autoimmune invasion by lymphocytes. In atrophic form, the resulting small gland causes severe hypothyroidism clinically.

Clinical Features

The clinical features of acquired hypothyroidism are listed in **Box 3**. Lethargy, fatigue, decreased activity, poor growth velocity and increased weight for height are frequent. The other common symptoms are dry skin and hair, constipation and cold intolerance. Unlike children with hyperthyroidism seen with poor concentration and lowered school performance, those with hypothyroidism have good academic scores (but may temporarily

BOX 3 Clinical features of hypothyroidism in children

Symptoms
- Lethargy; somnolence
- Low level of physical activity
- Normal or poor school performance
- Poor appetite but increased weight gain
- Dry skin
- Cold intolerance
- Constipation
- Delayed puberty
- Precocious puberty (rare)
- Family history of thyroid or autoimmune disorders

Signs
- Pallor
- Poor height velocity; short stature
- Increased weight for height
- Myxedema of face
- Goiter
- Absent or atrophic thyroid
- Bradycardia
- Cold extremities
- Decreased pulse rate
- Proximal myopathy
- Delayed relaxation phase of ankle jerk
- Delayed dentition
- Delayed puberty
- Delayed bone age.

deteriorate with initiation of thyroxine replacement). In many cases, symptoms and signs may have been present for months or years without being recognized.

Differential Diagnosis

Clinical diagnosis of hypothyroidism must be entertained in all of the following conditions: prolonged constipation, mood disorder (depression), short stature, malabsorption and malnutrition. Hypothyroidism will need also to be ruled out prior to making a diagnosis of constitutional growth delay or growth hormone deficiency.

Laboratory Tests

It is important to interpret thyroid function tests in children based on the normal range of hormone values for different ages **(Table 3)**. Low serum T4 (or free T4) and elevated serum TSH concentrations indicate primary hypothyroidism. T3 estimation is not useful as it may often be normal in hypothyroidism. If serum T4 or free T4 levels are low with normal or low serum TSH value, secondary or tertiary hypothyroidism should be suspected, but TBG deficiency should be ruled out. TRH stimulation test will help distinction between secondary and tertiary hypothyroidism. In secondary hypothyroidism, TRH will not elicit TSH response but in tertiary hypothyroidism, increased TSH response will be seen.

In CLT, anti-TG and anti-TPO antibody titers are increased and are useful markers for diagnosis. Ultrasonography, thyroid nuclear scan and fine needle aspiration cytology are indicated in the presence of a thyroid nodule. Children with predisposing factors such as type 1 diabetes mellitus, Down syndrome and conditions mentioned in **Box 2** should be monitored annually with thyroid function tests.

Histology of CLT demonstrates lymphocytic infiltration, formation of lymphoid follicles and follicular cell hyperplasia.

Management

Thyroxine replacement therapy using levothyroxine is the mainstay of treatment in hypothyroidism and with regular and continuous therapy; the symptoms disappear with remarkable overall improvement. The dose of levothyroxine for different age groups is given in **Table 4**.

Alternatively, a dose of 100 µg/m^2/day may also be used. The goal is to keep serum free T4 in the mid normal range and TSH in the normal range. Nearly 20% of children with CLT recover, become euthyroid and do not require lifelong thyroxine replacement. After attaining puberty, a 6-month trial of stopping thyroxine may be considered with serial measurements of free T4 and TSH every 3 months. In children with coexisting hypopituitarism or adrenal insufficiency or in those with chronic untreated hypothyroidism, glucocorticoid therapy should always precede thyroxine replacement to reduce the risk of adrenal crisis which may arise from enhanced metabolic needs induced rapidly by thyroxine replacement.

Prognosis

Prognosis is good if the diagnosis is made early without any delay and treatment begun. It also depends on the age at diagnosis and

Table 4 The dose of levothyroxine for different age groups

Age	Dose of thyroxine (µg/kg/day)
6–12 months	5–8
1–3 years	4–6
3–10 years	3–5
10–18 years	2–4

the duration of hypothyroidism. If symptoms were longstanding prior to therapy, recovery of physical stature is not always possible. Permanent intellectual or neurological deficits are less likely if age at diagnosis is beyond 3 years. Children with acquired hypothyroidism who receive adequate treatment at least 5 years before the onset of puberty may attain their genetic potential for final adult height.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism (SCH) is defined as a normal serum total or free T4 level and a mildly elevated TSH (typically 5–10 mU/L). While this is common in children, treatment is controversial since there are currently no specific guidelines on management. Several recent pediatric studies indicate that progression of SCH to overt hypothyroidism is uncommon and that over a period of several years, elevated TSH usually either normalizes or persists without rising and without the clinical picture of hypothyroidism emerging. The etiology appears to be multifactorial, with some cases representing minor developmental abnormalities, some related to obesity, some to mild autoimmune thyroiditis, and some associated with mutations in the gene for the TSH receptor. There are no conclusive pediatric studies showing clinical benefit of treating these children with thyroid hormone, but additional studies in this area are needed. Since few cases of pediatric SCH progress to overt hypothyroidism, treatment may be deferred and periodic follow-up testing undertaken. Elevated thyroid antibodies or presence of a goiter are being considered risk factors for development of eventual overt hypothyroidism. If over a period of 2 years, the thyroid profile remains stable without increase in serum TSH, further periodic monitoring is not required.

SICK EUTHYROID SYNDROME

In nonthyroidal conditions such as acute or chronic severe illness, surgery, trauma, fasting, malnutrition and use of certain drugs, the classic findings of low T4 and free T4, low T3 with a low or normal TSH are not uncommon. The finding of elevated reverse T3 will confirm this disorder. Thyroid hormone replacement is not needed because the disorder resolves with amelioration of the underlying disease.

The mechanism is as follows: T4 5'-deiodinase enzyme converts T4 in peripheral tissues to the active hormone T3 and also helps in clearing reverse T3, which is a byproduct of T4 metabolism. With several nonthyroidal disorders listed above, 5'-deiodinase activity is inhibited resulting in low T3 production and elevated reverse T3 level.

THYROIDITIS

Thyroiditis includes: (1) acute suppurative thyroiditis due to bacterial infection, (2) subacute thyroiditis following a viral infection and (3) chronic thyroiditis, usually autoimmune in nature and the most common of the three types mentioned here. Autoimmune thyroiditis has been discussed in detail under acquired hypothyroidism.

Acute suppurative thyroiditis mostly involves the left lobe of the thyroid and is caused by *Staphylococcus aureus, Streptococcus haemolyticus* and pneumococci but also occasionally by aerobic and anaerobic bacteria. It is rare in children. Painful thyroid suggests suppuration. It may progress to abscess formation, and hence if diagnosed promptly and with appropriate antibiotics, this can be avoided.

Acute thyroiditis presents with fever, malaise, swollen tender thyroid. Neck pain is often unilateral and radiates to the mandible, ears or occiput. Sore throat, hoarseness of voice and dysphagia are common. Leukocytosis with a shift to the left is common; ESR is elevated and thyroid function tests will demonstrate elevated serum T4 and T3 levels, released by the inflammation into the circulation. Unlike in Graves' disease, radioiodine tracer uptake is low. Ultrasonography will be useful to identify thyroid abscess. Treatment is by appropriate antibiotic cover and liberal use of anti-inflammatory drugs.

In *subacute thyroiditis*, initial symptoms occasionally may suggest hyperthyroidism. Low grade fever, weakness and signs of systemic illness may be present. It is usually self-limiting and only supportive measures such as anti-inflammatory drugs are used to reduce discomfort and provide relief. Propranolol can be used to reduce signs and symptoms of hyperthyroidism.

> ## IN A NUTSHELL
> 1. Normal values of thyroid function tests are age-specific and hence interpretation of results needs to be based on age range.
> 2. The aim of treatment is to preserve or achieve normal growth and cognitive outcome and hence prompt recognition and initiation of treatment with good compliance will be essential.

MORE ON THIS TOPIC

Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. J Thyroid Res. 2011;67:5703.

LaFranchi SH. Newborn screening strategies for congenital hypothyroidism: an update. J Inherit Metab Dis. 2010;33:S225-33.

LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. J Clin Endocrinol Metab. 2011;96:2959-67.

Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of congenital hypothyroidism. J Clin Endocrinol Metab. 2014;99:363-84.

Olivieri A, Corbetta C, Weber G, et al. Congenital hypothyroidism due to defects of thyroid development and mild increase of TSH at screening: data from the Italian National Registry of Infants with Congenital Hypothyroidism. J Clin Endocrinol Metab. 2013;98:1403-8.

Rapaport R. Congenital hypothyroidism: an evolving common clinical conundrum. J Clin Endocrinol Metab. 2010;95:4223-5.

Saravanan P, Dayan CM. Thyroid autoantibodies. Endocrinol Metab Clin North Am. 2001;30:315-37.

Schoen EJ, Clapp W, To TT, et al. The key role of newborn thyroid scintigraphy with isotopic iodide (^{123}I) in defining and managing congenital hypo-thyroidism. Pediatrics. 2004;114:e683-8.

Chapter 44.7
Newborn Screening for Congenital Hypothyroidism
Anna Simon

Newborn screening (NBS) is performed for diseases which are not evident clinically at birth, have serious irreversible consequences if treated late, have an excellent outcome if treated early, have a reliable diagnostic test, and available therapy. They should be common enough to justify economic costs. Screening for congenital hypothyroidism (CH) satisfies the prerequisites for a screening program. Unidentified CH has a significant negative impact on neurodevelopmental outcome, accurate biochemical assessments to confirm diagnosis are available and improved outcomes are definite with early intervention. It also is cost effective and acceptable to families. The high sensitivity and specificity of newer TSH assays make it a very useful screening test.

Neonatal thyroid screening is part of the national screening program in most developed countries. The incidence of CH is 1:3,000 to 1:4,000 as reported from countries where screening programs are ongoing over the last few decades. A higher prevalence has been reported from the Middle East and Asian countries and is likely in regions with severe iodine deficiency. Reports from India suggest that the incidence of CH in India is much higher than that reported in Western literature, approximately 1 in 1,100–1,200 newborns.

If the NBS program tests for other metabolic diseases, some of which require a specific metabolite to accumulate in the blood after feeding begins, then the most convenient specimen is blood from a heel-prick collected on special filter paper cards. This specimen is ideally collected between 2 days and 5 days of age (or at discharge from the hospital, if this occurs earlier). Cord blood TSH has also been used successfully for CH screening, especially when other diseases are not included in the NBS program. In this case, venous blood from an umbilical vein of the placenta can be collected in a vial (if serum TSH will be performed in the same hospital) or on filter paper (for transport to a central lab).

PRIMARY TSH SCREENING

Primary TSH screening is the most popular CH screening strategy nowadays because of the high sensitivity and specificity of TSH assays. Primary CH screening has been proved to be effective by using cord blood or blood collected after 36 hours of age (The physiological neonatal TSH surge precludes accurate interpretation of samples taken before 36–48 hours). Blood is spotted onto filter paper, allowed to dry and eluted into buffer for the analysis of TSH. A primary TSH test strategy will detect infants with mild or *subclinical* hypothyroidism but will not detect infants with secondary or central hypothyroidism and premature infants with *delayed TSH rise*.

PRIMARY T4 SCREENING

Many screening programs in USA undertake an initial primary T4 test, with a follow-up TSH. This primary T4 with follow-up TSH test strategy has the advantage of detecting some infants with secondary or central hypothyroidism and infants with *delayed TSH rise*.

COMBINED TSH AND T4 SCREENING

Combined TSH and T4 screening will have the advantage of detecting most cases of primary hypothyroidism, central hypothyroidism and babies with delayed TSH rise, but will be less cost effective.

CONFIRMATION OF SCREENING RESULTS

Once an infant has been detected with abnormal thyroid screening tests, they should be recalled immediately for examination, and a venous blood sample is obtained for confirmatory serum testing. Serum TSH and either free T4 or total T4 are estimated to confirm the diagnosis. It is important to compare the serum results with age normal reference ranges. The TSH can be as high as 39 mU/L in the first 72 hours due to the physiological TSH surge that occurs shortly after birth. Thereafter, the TSH values decline to an upper limit of 10 mU/L at 1–2 weeks of life. Nuclear imaging and ultrasound of the thyroid gland are useful to confirm the etiology and plan management. Estimation of thyroglobulin, TBG and maternal thyroid antibodies will help to further categorize the thyroid disorder. Several advanced laboratories also offer genetic mutational analysis to confirm both primary and secondary CH.

Confirmation of hypothyroid state before replacement is important to prevent the side-effects of unnecessary treatment with *l*-thyroxine. Treatment should begin latest by 2 weeks of age.

SCREENING IN SPECIAL CATEGORIES

Modified strategies and specific biochemical criteria should be used for screening of preterms, low birthweight babies and multiple births. This group of babies are at risk for transient and permanent CH. NBS programs should adapt cut-off values according to birthweight, gestational age, and age at sampling. As the hypothalamic-pituitary-thyroid axis is immature in preterm babies resulting in a delayed TSH rise, repeat and multiple sampling strategies should be instituted at regular intervals to screen for CH. The interpretation of screening results should take into account the results of all the specimens assayed in a multiple sampling.

IN A NUTSHELL

1. The high sensitivity and specificity of newer TSH assays make it a very useful screening test for CH.
2. The specimen is ideally collected between 2 days and 5 days of age on a filter paper.
3. Confirmation of hypothyroid state before replacement is important to prevent the side-effects of unnecessary treatment with *l*-thyroxine.
4. Treatment should begin latest by 2 weeks of age.
5. Modified strategies and specific biochemical criteria should be used for screening of preterms, low birthweight babies and multiple births.

MORE ON THIS TOPIC

American Academy of Pediatrics, Rose SR, Section on Endocrinology and Committee on Genetics, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006;117:2290-303.

Desai MP. Congenital hypothyroidism: Screening dilemma. Indian J Endocrinol Metab. 2012;16:S153-5.

Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab. 2014;28:175-87.

LaFranchi SH. Screening preterm infants for congenital hypothyroidism: better the second time around. J Pediatr. 2014;164:1259-61.

Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab. 2014;99:363-84.

Chapter 44.8
Hyperthyroidism
Sobha Kumar

Hyperthyroidism is a rare form of thyroid disorder in children, in contrast to hypothyroidism. Patients present with over-activity of basal metabolism due to overproduction of thyroid hormone.

EPIDEMIOLOGY

In an epidemiological study from Cochin (Kochi), subclinical and overt hyperthyroidism were present in 1.6% and 1.3% of subjects participating in a community survey. In a hospital-based study of women from Puducherry, subclinical and overt hyperthyroidism were present in 0.6% and 1.2% of subjects. More than a third of community-detected hyperthyroid cases had positive antithyroid peroxidase (TPO) antibodies, and about 39% of these subjects had a goiter. Graves' disease (GD) is the most common etiology (seen in 90% of cases), other causes being rare **(Box 1)**.

GRAVES' DISEASE

Graves' disease is an autoimmune condition, occurring due to the production of thyroid-stimulating immunoglobulins, which stimulate the thyroid-stimulating hormone (TSH) receptor. GD occurs in genetically predisposed individuals. Predisposition to GD is associated with the major histocompatibility complex, the high-risk alleles being HLA B8, HLA DR-3 and less commonly HLA DQA1. There is a female preponderance, the female-to-male prevalence ratio being 6:1. It is more common in adolescence, but the disease is more severe in prepubertal children.

Other autoimmune diseases that can be associated with GD are type 1 diabetes mellitus, Addison disease, systemic lupus erythematosus, and myasthenia gravis. Syndromes associated with GD include Down syndrome and rarely DiGeorge syndrome.

Pathogenesis

The TSH receptor antibody mimics the action of TSH on its receptor and causes stimulation of adenyl cyclase which in turn causes thyroid hormonogenesis and growth. Hyperthyroidism and thyromegaly of GD are mediated through immunoglobulin G (IgG1) that binds to the extracellular domain of the TSH receptor and stimulates follicular cell growth and function. The major source of TSH receptor antibody production appears to be intrathyroidal lymphocytes, lymphocytes in spleen, lymph nodes, bone marrow and peripheral blood.

The proposed mechanism and control of stimulating TSH receptor antibody production include deficiency of specific suppressor T-cell function, breakdown of idiotype and anti-idiotype network of β-lymphocytes immune regulation, and increased frequency of antibodies to certain serotypes of *Yersinia enterocolitica*.

BOX 1 Causes of thyrotoxicosis in children

- Graves' disease and Hashimoto hyperthyroidism
- Toxic adenoma (autonomously functioning thyroid nodule)
- Toxic multinodular goiter including functional nonimmune hyperthyroidism and McCune-Albright syndrome
- Acute and subacute thyroiditis
- Neonatal thyrotoxicosis
- Thyrotoxicosis factitia (thyroid-hormone overdose)
- Central hyperthyroidism (TSH-producing adenoma)
- Thyroid-hormone resistance

Clinical Features

The symptoms include increased appetite, weight loss despite increased food intake, tremors, irritability, inability to sleep, proximal muscle weakness, headache and palpitations. Shortened attention span and emotional lability may lead to severe behavioral and school difficulties. Other symptoms include polyuria and nocturia, increase in linear growth and secondary amenorrhea.

The thyroid is diffusely enlarged, and the gland is soft, fleshy and smooth with a bruit. The hair texture is fine. Excess activity manifests as fidgetiness. There is a fine tremor of the tongue and fingers. Tachycardia and a wide pulse pressure are typical. Young children can manifest with diarrhea, transitory language delay, or craniosynostosis.

Eye abnormalities include signs of sympathetic hyperactivity (lid lag, lid retraction and globe lag) and those of infiltrative ophthalmopathy characterized by exophthalmos **(Fig. 1)**, conjunctival chemosis or edema, lid edema, and conjunctival redness; and in severe cases ophthalmoplegia, periorbital ecchymosis, diplopia, uveitis, and corneal ulceration. Accumulation of glycosaminoglycans in connective tissue components of orbital fat and muscles, extraocular muscle dysfunction, edema, inflammation, and fibrosis of endomysial connective tissues contribute to symptoms. Orbital antigens share unique structural characteristic with antigens of thyroid gland. Eye findings are less severe in children as compared to adults with thyrotoxicosis and improve in association with control of hyperthyroidism. Severe cases are treated with oral corticosteroids, orbital irradiation and surgical decompression.

Other features which point to an autoimmune origin are associations with vitiligo, systemic vasculitis, Addison disease, type 1 diabetes mellitus, myasthenia gravis, and pernicious anemia.

Laboratory Investigations

Thyroid-stimulating hormone (second- or third-generation assay) is suppressed and T4 or free T4 is elevated. Serum T3 is useful at the time of diagnosis, as some patients may have only elevated T3 and not T4. TSH receptor antibody test if available will be found to be positive. Baseline complete and differential WBC and serum alanine aminotransferase (ALT or SGPT) may be relevant as these are often abnormal due to GD itself, and if shown to be so before start of therapy, will not be taken as indicative of adverse effects of antithyroid medication. Thyroglobulin and TPO antibodies are present in thyrotoxicosis due to Hashimoto thyroiditis and subacute thyroiditis.

Treatment

Initial treatment is by the antithyroid drugs (ATD) such as methimazole, carbimazole, or propylthiouracil (PTU). They act by

Figure 1 Girl with Graves' ophthalmopathy showing exophthalmos and lid retraction

blocking the incorporation of oxidized iodide into tyrosine residues of thyroglobulin which serves as substrate for TPO. PTU also inhibits the peripheral conversion of T4 to T3, and hence is very useful for initial treatment of severe hyperthyroidism. However, due to the increased occurrence of hepatotoxicity with PTU than with other ATD, this drug is best avoided. After starting the drugs, thyroid hormone levels should be retested after 4–6 weeks' intervals till the patient becomes euthyroid. Maintenance therapy is given for 18–24 months, either by gradually reducing the dosage of ATD to maintain thyroid hormone levels in the normal range, or adding *l*-thyroxine to therapy when the ATD have rendered the child hypothyroid (the block and replace regimen). The latter may be accompanied more often by adverse effects and is, therefore, less often chosen.

Agranulocytosis is a rare but important adverse effect of ATD. Standing instructions to the family should be that the occurrence of fever or sore throat should prompt the temporary cessation of medication and the performance of blood counts. The drug is to be discontinued below absolute neutrophil count of 1,000/mm^2. Cross-reactivity between PTU and methimazole for agranulocytosis is possible; hence, use of an alternative antithyroid drug is contraindicated. Systemic vasculitis is another rare major complication of thionamide, more often associated with PTU.

Remission occurs in about 30–40% of children, less in younger children. If a relapse occurs at the end of prolonged medical therapy, a permanent method of ablation such as surgery or radioactive iodine is opted for. Radioiodine ablation is not chosen for young children below about 10 years of age. Surgery is also recommended for very large goiters or in case of suspected malignancy.

OTHER CAUSES OF HYPERTHYROIDISM

Autonomously Functioning Thyroid Nodule

This is a thyroid nodule functioning independently of the pituitary axis. This can result from somatic gain-of-function mutation of TSH receptors. Radionuclide imaging is diagnostic and radioiodine ablation after initial medical management is highly successful.

Functional Nonimmune Hyperthyroidism

This cause of a toxic multinodular goiter occurs due to a gain of function mutation leading to activation of TSH receptor G-protein effector system. Functional nonimmune hyperthyroidism (FNH) accounts for 2–5% of all cases diffuse hyperthyroidism. It is transmitted in an autosomal dominant fashion. Thyrotoxicosis in McCune-Albright syndrome presents similarly; however, it occurs due to a somatic mutation, and family history will be negative. Prematurity and low birthweight are constant features. Initial antithyroid therapy is followed by surgery. However, regrowth often occurs both in FNH and McCune-Albright syndrome, and hence, radioablation is usually necessary.

Thyroid-stimulating Hormone-induced Hyperthyroidism

This may occur due to a TSH secreting pituitary adenoma or due to selective pituitary resistance to thyroid hormone. The latter is an autosomal dominant condition, and is characterized by an increase in peripheral metabolism, diffuse thyromegaly, increase in T4, and elevated TSH inappropriate to T4 levels. Differentiation from a pituitary tumor is important. The ratio of alpha subunit/TSH is > 1 in a pituitary tumor and < 1 in pituitary resistance to thyroid hormone.

Exogenous Thyroxine

Ingestion of thyroxine in excessive quantities leads to *thyrotoxicosis factitia*, characterized by fever, tachycardia, vomiting and hyperactive behavior. Thyromegaly is absent. Plasma thyroglobulin levels are undetectable or extremely low, which differentiates this from other causes of hyperthyroidism. Beta-adrenergic blockade is helpful in controlling tachycardia. In more severe cases, iopanoic acid or glucocorticoid can be used to decrease T4 to T3 peripheral conversion.

NEONATAL THYROTOXICOSIS

This occurs due to transplacental passage of TSH receptor antibodies. Prematurity, intrauterine growth restriction, irritability, tachycardia, wide open eyes, microcephaly with fused sutures, increased feed intake with failure to thrive, hepatosplenomegaly, goiter, and jaundice are the main manifestations. Prenatal diagnosis can be performed by documentation of fetal goiter and tachycardia. This is a transient condition, which abates with the diminution of maternal immunoglobulin levels at about 3–4 months of age. Treatment includes propranolol and methimazole. Corticosteroids can be used in severe cases.

THYROTOXIC EMERGENCIES

Thyroid Storm

This is a life-threatening emergency characterized by fever, tachycardia, high output cardiac failure, vomiting and diarrhea. Common neurological symptoms include confusion, obtundation seizures and coma. Precipitating features include trauma, ingestion of sympathomimetics, infection, iodine therapy and discontinuation of therapy with ATD.

Treatment Mortality is high (80–90%) if not recognized and treated. Treatment includes care of respiratory and cardiac factors, and the use of ATD, adrenergic blocking agents and glucocorticoids.

Thyrotoxic Periodic Paralysis

This manifests as sudden onset of weakness involving proximal muscles. Cardiac rhythm abnormalities are common. Rhabdomyolysis is a possibility. Precipitating events are high carbohydrate diet and exercise. Lab evaluation shows high T3 and T4 with suppressed TSH and hypokalemia. Possibilities as to the cause are alteration of the plasma membrane permeability to potassium and sodium and intracellular shift of potassium.

Management The child should be admitted to the hospital and managed by judicious supplementation of potassium.

IN A NUTSHELL

1. Hyperthyroidism is a rare disorder in children.
2. Graves' disease, caused by TSH receptor antibodies, forms 90% of cases of hyperthyroidism.
3. Initial clinical features are vague but ophthalmopathy and goiter are constant features.
4. Other causes include toxic adenoma, multinodular goiter, pituitary tumors and resistance, and exogenous thyroxine.
5. Treatment options include ATD, radioiodine ablation and surgery.

MORE ON THIS TOPIC

Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21:593-646.

Brown RS. Disorders of the thyroid gland in infancy, childhood and adolescence. In: de Groot LJ. Thyroid Disease Manager. From www.thyroidmanager.org. Accessed on August 28, 2014.

Leger J, Gelwane G, Kaguelidou F, et al. Positive impact of long term antithyroid drug treatment on the outcome of children with Graves' disease: national long term cohort study. J Clin Endocrinol Metab. 2012;97:110-9.

Menon PSN Hyperthyroidism. In: Desai MP, Menon PSN, Bhatia V. Pediatric Endocrine Disorders, 3rd ed. Hyderabad: Universities Press; 2014. pp. 211-4.

Chapter 44.9
Goiter and Nodules
Lalitha Kailas, Riaz I

A goiter is an enlargement of thyroid gland which can be diffuse or nodular and could be due to varied causes. Diffuse swellings could be idiopathic in nature in many children but dyshormonogenesis as well as thyroiditis could also manifest with diffuse goiter. Nodular goiters are rare in children and carry a higher risk for malignancy than in an adult. In all cases of goiters in children, a proper evaluation focused on the etiology and proper management is warranted.

EPIDEMIOLOGY

A recent study puts population prevalence of goiter at 12% among adults in South India. Universal iodization of salt is well proven to be effective by bringing down the incidence in some areas by almost one-fifth.

ETIOLOGY

Chronic autoimmune thyroiditis otherwise called Hashimoto thyroiditis is by far the most common cause of thyroiditis among children **(Box 1)**. It is characterized by presence of high levels of thyroid autoantibodies with or without thyroid dysfunction. Thyroid-stimulating antibodies in Graves' disease cause hyperplasia of the follicular cells, subsequent goiter and hyperthyroidism. Lymphocytic infiltration of the gland is common to both above mentioned entities. Suppurative thyroiditis and painful subacute thyroiditis are less common causes.

Inborn errors of metabolism due to partial or complete dysfunction of enzymes and channels involved in thyroid hormone synthesis or dyshormonogenesis can present with goiter with or without hypothyroidism. Even though three-fourth of the salt marketed in the country contains adequate amounts of supplemental iodine, endemic goiter is still seen in some areas. Antithyroid drugs taken by the mother during pregnancy is a cause of goiter in the newborn.

Thyroid nodules are rare in children. Detecting a nodule in a child is more important as the chance of malignancy is as high as five times compared to adults. Thyroid nodule in a child could be either a solitary nodule or more commonly a prominent nodule in a multinodular goiter.

PATHOPHYSIOLOGY

Goitrogenesis is an adaptation to any process which leads to decreased synthesis of thyroid hormones which stimulates the pituitary to produce more thyroid-stimulating hormone (TSH). Thyroid-stimulating hormone is the most important stimulating factor for growth and hyperplasia of follicular cells. The TSH receptor stimulating antibodies stimulate thyrotropin receptors leading to thyromegaly in children with Graves' disease.

Inflammation and infiltration of the gland causes the enlargement in conditions such as Hashimoto thyroiditis (lymphocytic infiltration). In some children, Hashimoto goiter could be the initial presentation of autoimmune polyendocrinopathy syndrome. Recent evidence suggests an increased risk of lymphoma in patients with Hashimoto disease. However, primary lymphoma of the thyroid gland is an exceedingly rare condition.

Colloid nodule, thyroid neoplasia and autonomously functioning toxic nodule can manifest with a single nodule.

CLINICAL FEATURES

Children with goiter can present with features of hypothyroidism, hyperthyroidism or in euthyroid status. Family history of goiter and thyroid dysfunction should be asked for in all children presenting with thyromegaly. Dyshormonogenesis in many cases is transmitted in an autosomal recessive pattern. Family history of thyroiditis is to be sought for when we are evaluating an older child with autoimmune thyroiditis.

Goiter presenting in a young child (< 3 years) could be the result of a congenital problem in most cases **(Fig. 1)**. Pendred syndrome is caused by a mutation in the *pendrin* gene affecting the transport of ions in the follicular cell as well as in the inner ear resulting in hypothyroidism, goiter and sensory neural deafness. So, it is a good practice to do a hearing assessment test in all infants presenting with goitrous hypothyroidism, in case universal screening is not available. A history of radiation to the head and neck is relevant due to the high incidence of thyroid malignancy in the follow-up of these children. Residence in an area of known endemicity for iodine deficiency is an important history to elicit.

An older child presenting with a symmetric diffuse firm swelling of the gland with the typical bosselated appearance most probably has Hashimoto thyroiditis **(Fig. 2)**. Idiopathic

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BOX 1   Common causes of thyromegaly in children

Congenital causes
- Dyshormonogenetic goiter
- Maternal iodine deficiency/intake of antithyroid drugs or goitrogens
- Transplacental transfer of maternal antibodies
- Hemiagenesis of thyroid

Acquired causes
- Hashimoto thyroiditis
- Subacute thyroiditis
- Goitrogens: cassava and brassica vegetables
- Endemic goiter
- Colloid goiter (simple goiter)
- Graves' disease
- Reidel's thyroiditis
- Nodular thyromegaly
  - Hyperfunctioning nodules
  - Hypofunctioning nodules
    - Colloid nodule
    - Benign adenoma
    - Papillary carcinoma
    - Follicular carcinoma.

Figure 1 Hemiagenesis of the left lobe of the thyroid, presenting as a nodular goiter

Figure 2 Diffuse enlargement in a girl with Hashimoto thyroiditis

(colloid) goiters can also be seen in children. In children who have associated thyroid dysfunction features of hypothyroidism will be seen. Mental retardation in a child with goiter points to congenital nature of the disease and the possibilities are endemic iodine deficiency cretinism and dyshormonogenesis. Diffuse goiter in the newborn may be due to Graves' disease, dyshormonogenesis, or goitrogenic drugs.

Toxic goiters are those presenting with signs and symptoms of hyperthyroidism. Graves' disease and toxic phase of Hashimoto thyroiditis present with smooth thyromegaly with enhanced radiotracer uptake on a radionuclide thyroid scan. Hyperthyroid thyromegaly is discussed in more detail in the section on hyperthyroidism.

The examination of the gland should be done both by visual assessment and palpation; a simple grading scheme put forward by the WHO can be used for assessing the size of the goiter **(Box 2)** at diagnosis and during follow-up. One should also remember the definition of goiter '*lobes larger than the terminal phalanx of*

BOX 2 WHO classification of goiter

- *Grade 0:* No goiter is present (the thyroid impalpable and invisible)
- *Grade 1:* Neck thickening is present in result of enlarged thyroid, palpable, however, not visible in normal position of neck; the thickened mass moves upward during swallowing. Grade 1 includes also nodular goiter if thyroid enlargement remains invisible.
- *Grade 2:* Neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid found in palpation

the patient's thumb'. While examining one should look for size, consistency, symmetry, diffuse or nodular nature and regional lymphadenopathy. Head to foot examination and systemic examination should be properly performed paying attention to look for signs of both hypothyroidism and hyperthyroidism.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

In any child with a goiter, the functional status of the thyroid gland must be assessed, with either total or free T4, TSH, antithyroid antibodies (antithyroid peroxidase antibody, TPO, or antithyroglobulin, TG, antibodies), and T3 in addition if suspecting thyrotoxicosis **(Flow chart 1)**. High titers of anti-TPO or/and anti-TG along with a diffuse enlargement of the gland points to a diagnosis of Hashimoto thyroiditis. It may or may not be associated with hypothyroidism. Suppressed TSH with elevated T4, FT4 or T3 suggests a diagnosis of Graves' disease. The specific antibody for Graves' disease, namely TSH receptor antibody (TRAb) cannot be measured in routine care and is not essential for making a diagnosis.

In children who test negative for the antibodies and have a euthyroid status biochemically a diagnosis of simple (colloid) goiter can be kept. Iodine sufficiency could be evaluated by measuring the urinary iodine excretion and a proper diet and drug history to assess the role of goitrogens should be obtained before stamping the diagnosis of colloid goiter. In younger children, who are antibody negative, it is prudent to evaluate for congenital causes by ultrasonography and scintigraphy studies.

Flow chart 1 Approach to a child with goiter
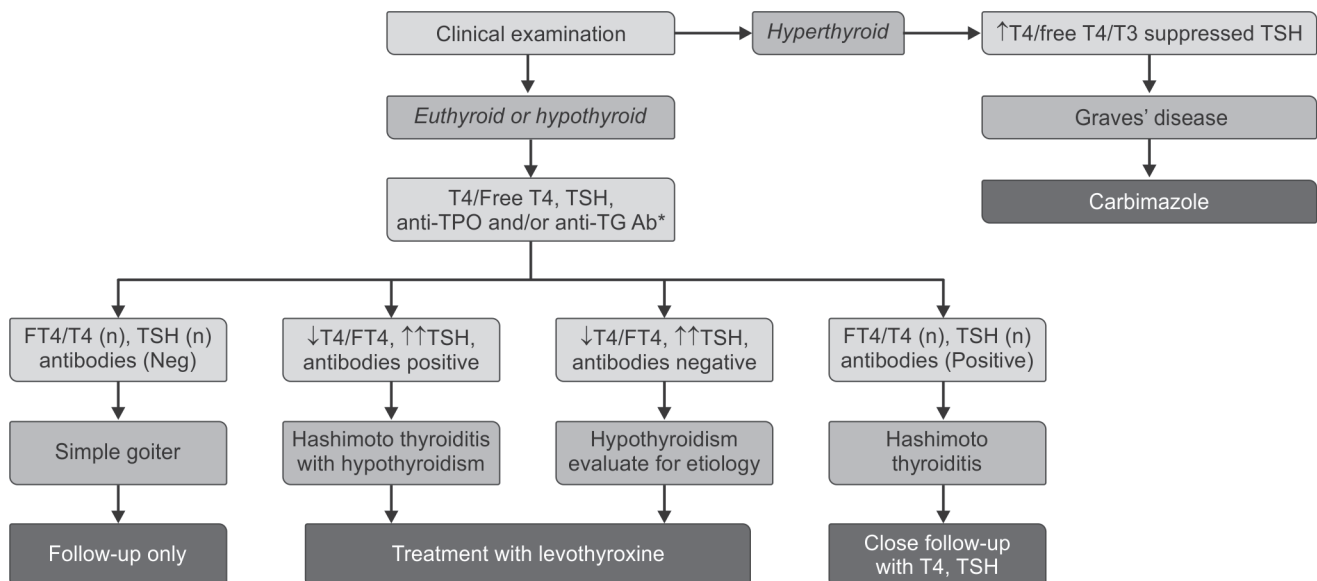
*In children < 3 years of age as autoimmunity is rare and congenital anomalies are common, ultrasonography and nuclear scan (to identify dyshormonogenesis) should be considered in the place of antibody tests

Flow chart 2 Evaluation of a thyroid nodule
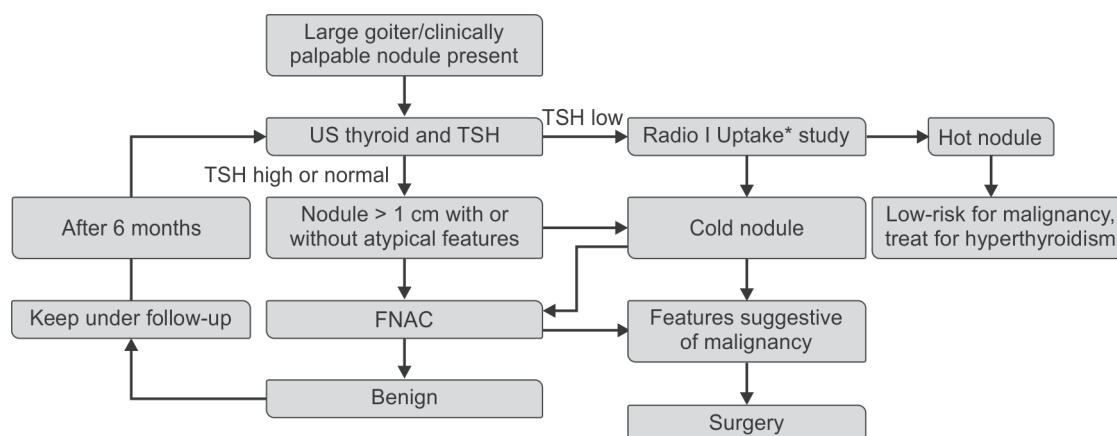
*[123]I is the preferred isotope for doing a radioiodine scan in children, but as it is not easily available in India, most centers use technetium pertechnetate for a scan and ^{123}I for uptake studies

An ultrasound scan could identify a hemiagenesis and sometimes a dysgenetic small gland. Performing a radioiodine uptake scan followed by a perchlorate discharge test will confirm the diagnosis dyshormonogenesis. Scarce availability of ^{123}I, the isotope preferred for imaging studies in children is a main hindrance in performing this test in our country.

Any clinically palpable nodule or a nodular goiter should prompt the pediatrician to request an ultrasound examination to assess the shape and borders of the nodule, its echogenicity and presence of cystic or solid areas, presence of microcalcifications, or lymph nodes. Ultrasound-guided fine needle aspiration cytology (FNAC) is indicated in euthyroid cases with nodule **(Flow chart 2)**. The risk of malignancy is around five times in children compared to adults (18–25% vs 5%).

TREATMENT

Treatment strategies for goiter in children depend on factors including etiology, presence of thyroid dysfunction, nodularity, etc.

In *hypothyroid children with goiter*, treatment with levo-thyroxine will lead to normalization of TSH and gradual decease in the size of goiter in most cases. Children with Graves' disease should receive antithyroid medication. The reader is referred to the accompanying sections for details regarding treatment of hypo- and hyperthyroidism. The condition of subclinical hypothyroidism deserves special mention. One often encounters mildly elevated TSH with a normal T4 or FT4, both in children and adults. The majority of these *subclinical hypothyroid* states revert back to normal or remain the same on follow-up. Those associated with a goiter or with antithyroid antibodies are more likely to progress to overt hypothyroidism requiring thyroxine replacement. The 97th percentile of TSH in school age children was estimated to be 6.01–8.4 mU/L for boys and 5.28–8.04 mU/L for girls in a recent survey. Therefore, a cut-off TSH of 10 mU/L could be used in children when deciding to treat subclinical hypothyroidism.

In a biochemically *euthyroid child with goiter*, treatment with thyroxine will not help much in decreasing the gland size even if antithyroid antibodies are positive; only follow-up is indicated. A natural history study of such a cohort showed after 20 years, 60%

people were normal, 20% unchanged and a few (10%) developed chronic thyroiditis.

Children with thyroid nodules of significant size (> 1 cm) should undergo fine needle aspiration cytology, preferably ultrasound-guided and if features suggestive of malignancy are present, surgical intervention, followed by suppressive therapy with levothyroxine, is the standard line of care. Degree of cure and absence of recurrence both can be monitored by regular monitoring of serum TG levels in these children.

Nodules with benign cytology can be followed up regularly with 6 monthly ultrasonography of the thyroid to assess the size of the nodule and also FNAC if needed. Large nodules may need surgical removal.

IN A NUTSHELL

1. Children with goiter may be euthyroid, hypothyroid or hyperthyroid.
2. Simple goiter with no thyroid dysfunction needs only observation and follow-up. Closer follow-up is indicated in those positive for antithyroid antibodies.
3. Nodular goiter/single nodule needs careful evaluation for presence of thyroid malignancy.

MORE ON THIS TOPIC

Desai MP. Hypothyroidism, goitre and thyroid neoplasia. In: Desai MP, Menon PSN, Bhatia V. Pediatric Endocrine Disorders, 3rd ed. Hyderabad: Universities Press; 2014. pp. 194-210.

Huang SA. Thyromegaly. In: Lifshitz F. Pediatric Endocrinology, 5th ed, Vol 2. New York: Informa Healthcare; 2007. pp. 443-53.

Kaplowitz PB. Subclinical hypothyroidism in children: normal variation or sign of a failing thyroid gland? Int J Pediatr Endocrinol. 2010;2010:281453.

Muirhead S. Diagnostic approach to goiter in children. Paediatr Child Health. 2001;6:195-9.

Unnikrishnan AG, Kalra S, Baruah M, et al. Endocrine Society of India management guidelines for patients with thyroid nodules: a position statement. Indian J Endocrinol Metab. 2011;15:2-8.

Unnikrishnan AG, Usha VM. Thyroid disorders in India: an epidemiological perspective. Indian J Endocrinol Metab. 2011;15 (Suppl 2):S78-81.

Chapter 44.10
Normal Puberty
Ruchi Parikh, Meena Desai

Puberty is the phase of transition from the sexually immature child to the mature, potentially fertile adolescent and adult. The term puberty is derived from the Latin word *puberatum*, meaning the age of maturity. Normal pubertal development requires close integration of the hypothalamic-pituitary-gonadal (HPG) axis and the adrenal cortex. The HPG axis which is in abeyance during childhood plays a crucial role in promoting physical changes of puberty with development of secondary sex characters, growth spurt and maturation of gonads in both boys and girls. Pubertal changes usually follow a sequential pattern.

The common terminologies related to puberty are described in **Table 1**.

EPIDEMIOLOGY

Though genetics and ethnicity play an important role, the epidemiology of puberty in India and South Asia relates to adverse factors like prevalence of malnutrition, chronic diseases, socioeconomic conditions, and other environmental factors.

Age at onset of puberty is highly variable, usually between 8 and 13 years in girls and 9 and 14 years in boys. It is influenced by optimal nutrition and weight gain during midchildhood besides genetic and environmental conditions. The age at onset correlates better with skeletal maturation than with chronological age. The average age at menarche has shown a secular trend in most affluent countries. In urban Indian girls, it has decreased to 12.6 years over last 200 years but seems to have stabilized now. For rural Indian girls, it is still around 15–16 years. The age at thelarche has also decreased in recent years, especially in Caucasian and African-American girls. In boys, the age at onset of puberty as observed by attainment of testicular volume more than 4 mL has not shown a definitive secular trend. Industrial chemical effluents and pesticides have been demonstrated to act as endocrine disruptors influencing the age at onset of puberty.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

The endocrine reproductive system consists of the hypothalamus, pituitary gland, gonads (testis and ovary) and adrenal glands with input and regulation from many other body systems **(Fig. 1)**. The HPG axis controls and synchronizes pubertal development. The maturation of adrenal glands is an independent but interrelated process. The HPG axis is functional by the end of first trimester of fetal life. Gonadotropin-releasing hormone (GnRH) acting as

Table 1 Terminologies related to puberty and their description

Terminology	Description
Adrenarche	Onset of adrenal androgen production
Thelarche	Onset of breast development (breast bud)
Pubarche	Onset of pubic hair growth in both boys and girls
Menarche	First menstrual period
Gonadarche	Onset of pubertal maturation of gonads and secretion of sex hormones responsible for breast development and labial growth in girls and penile growth in boys
Spermarche	Appearance of sperms in seminal fluid

pulse generator in the hypothalamus is the key regulator of puberty. In the fetus, it is insensitive to the negative feedback by gonadal hormones (estrogen and testosterone) because of immaturity of the central nervous system (CNS); hence, the axis functions at pubertal level. Later in gestation, high levels of estrogen produced by the maternal-placental-fetal unit suppress the HPG axis activity. After delivery, owing to maternal estrogen withdrawal, pituitary gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] increase leading to *minipuberty* in the newborn, which leads to postnatal phallic growth and transient breast enlargement. Thereafter, gonadotropin levels decline gradually by 4 months. This, along with CNS maturation and increase in number of hypothalamic estrogen/dihydrotestosterone receptors accounts for increased receptiveness to inhibitory signals from hypothalamus. This explains the dormancy of the axis in midchildhood.

PHYSIOLOGY OF NORMAL PUBERTAL DEVELOPMENT

Hormonal Changes during Puberty

During late childhood, decrease in the sensitivity of the hypothalamic gonadostat to the sex hormone negative feedback permits the onset of puberty **(Fig. 1 and Flow chart 1)**. Nearly 1–3 years prior to onset of clinically evident puberty, LH release occurs during sleep. This is followed by progressive increase in frequency and amplitude of LH pulses extending through 24 hours by midpuberty.

Gonadotropins act on specific cells in the gonads. In girls, LH stimulates theca cells and FSH stimulates granulosa cells of the ovary to produce estradiol. This leads to breast development and maturation of reproductive system with initial thickening and shedding of endometrial lining causing menarche. Regular cyclic variation of estrogen and progesterone is characteristic of menstrual cycle and triggers ovulation. In boys, LH stimulates Leydig cells to secrete testosterone which leads to genital growth and FSH stimulates Sertoli cells of the testis to bring about gametogenesis and gonadal growth.

Adrenarche is due to maturation of the enzymes in zona reticularis of the adrenal cortex. This leads to increased adrenal androgen production, i.e., dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). It occurs between 6 and 8 years of age, nearly 2 years before gonadarche. Adrenal androgens are responsible for the pubic and axillary hair development, adult type odor, oily skin and acne in both girls and boys.

The sex hormones also stimulate epiphyseal growth and maturation and growth spurt, but estrogen is primarily responsible for epiphyseal fusion, cessation of growth and increased amplitude of growth hormone-insulin-like growth factor (GH-IGF-1) production which helps pubertal growth spurt.

Regulation of Onset and Progression of Puberty

The precise mechanism by which neuroendocrine and genetic factors regulate pubertal onset and normal progression remains unknown. GnRH pulse generator in the hypothalamus is the key regulator in its initiation. It involves a complex interplay between inhibitory and stimulating factors influenced by genetic, familial, ethnic factors as well as nutrition and environmental conditions.

Decrease in inhibitory factors like GABAergic and opioidergic mechanisms, neuropeptide-Y and increase in the stimulatory factors like glutamate, leptin, GH-IGF system and growth factors are the major proximate changes involved in the onset of puberty **(Flow chart 2)**. Activation of G-protein-coupled receptor 54

Figure 1 Schematic representation of hypothalamic-pituitary-gonadal axis and its action
Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Flow chart 1 Flowchart illustrating physiology of maturation of HPG axis and onset of puberty

Increasing pulsatile secretion of GnRH by the arcuate nucleus of the hypothalamus, initially during sleep

Increasing sensitivity of pituitary gonadotropic cells to GnRH

Increasing sensitization of gonads to gonadotropin stimulation

Sustained rise in sex hormone levels

Autoamplification of response at all levels of HPG axis

Set point for gonadotropin release encompass positive feedback mechanism

Flow chart 2 Hypothalamic pituitary gonadal axis and its regulation in puberty
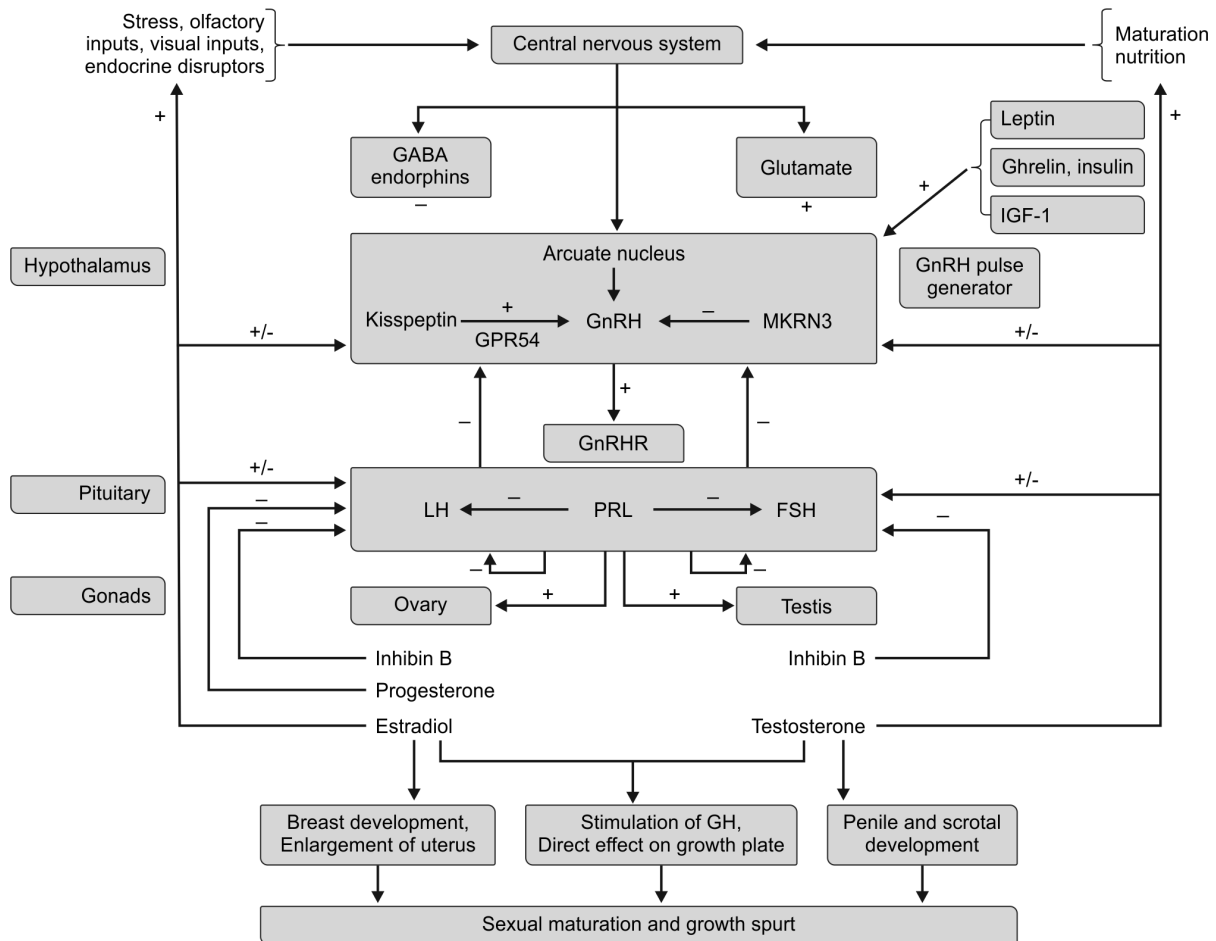
Central nervous system (CNS) relinquishes its inhibitory control over GnRH secretion by achieving high level of maturity. Neurons and neurotransmitters in the arcuate nucleus of the hypothalamic GnRH pulse generator coordinate GnRH release along with various inhibitory and stimulatory factors. Sex steroids are the main regulators of HPG axis feedback. Inhibin B, secreted by Sertoli cells of the testis and granulosa cells of the ovary, inhibits FSH secretion. Gonadotropins exert feedback effect on GnRH and their own release. This complex interplay of hormones brings about sexual maturation and growth spurt via the release of sex steroids from gonads in both boys and girls. Regulation may be either stimulatory (+) or inhibitory (–).

Abbreviations: FSH, follicle-stimulating hormone; GABA, gamma-amino butyric acid; GnRH, gonadotropin-releasing hormone; GnRHR, gonadotropin-releasing hormone receptor; GPR54, G-protein-coupled receptor 54; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; MKRN3, Makorin ring finger protein 3; PRL, prolactin

(GPR54) by its ligand kisspeptin stimulates LH and FSH release via the activation of GnRH. Leptin is secreted by adipocytes and acts on hypothalamus to reduce appetite and stimulate gonadotropin secretion. Other factors that link nutrition and puberty are glucose, ghrelin and insulin. GH facilitates the onset and tempo of puberty. Pituitary GnRH receptors (GnRHR) are downregulated by GnRH itself, and inhibins and sex steroids, whereas gonadotropins (LH and FSH) inhibit GnRH and their own release. This knowledge is utilized in the treatment of the disorders of puberty.

PHYSICAL CHANGES OF PUBERTY

The standard clinical system for describing normal pubertal development, which includes the somatic and physiologic changes, is the 5-stage system described by Tanner and Marshall. Stage 1 indicates prepubertal and stage-5 adult pattern **(Tables 2 and 3)**.

Onset of puberty in females is manifested by appearance of breast bud (thelarche), at an average age of 10.2 years. Usual sequence of progression is thelarche–pubarche–menarche, wherein the mean interval between thelarche and menarche is 2.3 ± 1 year. Peak height velocity (PHV) occurs in early adolescence at stage 3 of breast development and linear growth generally stops by 14–16 years. Estradiol is responsible for increase in subcutaneous body fat mass with growth of the pelvis and increase in interischial distance.

The first sign of puberty in boys is demonstrated by enlargement of testis with a gonadal volume of 4 mL with Prader's orchidometer or greater than or equal to 2.5 cm in length at a mean age of 11.5 years. This is followed by pubarche and spermarche. Testosterone leads to increased lean muscle mass and broadening of shoulders. PHV occurs in midpuberty, in contrast to girls, at genital stage 4 and linear growth is completed by 16–18 years.
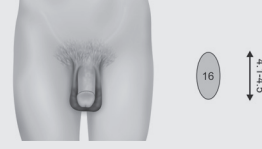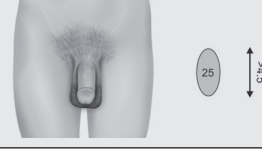
There is progressive increase in bone mineral density (BMD) during puberty which is maintained by estradiol and testosterone in both the boys and girls. Peak bone mass is achieved in early third decade of life with bone mass content maximally accrued during peak height velocity period. Thereafter, there is decline of bone mass in adulthood, at a rate of approximately 1–2% each year.

Table 2 Sexual maturity rating by Tanner's staging in girls and linear growth in puberty

Tanner stage	Breast development (B)	Pubic hair development (P)	Illustrations of B and P	Linear growth	Other changes	Internal genitalia
Stage 1	Prepubertal—Elevation of papilla only	Prepubertal vellus hair only		Prepubertal: 5–6 cm per year	Adrenarche	Ovarian volume: 0.3–0.9 cm³ Ut length: 2–3 cm Ut/Cx ratio: 1:1
Stage 2	Breast bud appears under an enlarged areola	Sparse hair along labia		Accelerated growth: 7–8 cm per year	Clitoral enlargement with labial pigmentation Few axillary hairs	Ovarian volume: 1 cm³ Ut enlargement
Stage 3	Breast tissue grows beyond areola but without contour separation	Hair coarser, pigmented and curled—spreads across pubes		Peak height velocity (PHV): 7–9 cm per year	Axillary hair: adult pattern (A) Acne	
Stage 4	Areola and nipple form a secondary mound above the level of the breast	Adult pattern but without spread to medial thigh		Deceleration, less than 7 cm per year	Menarche	
Stage 5	Adult breast contour with projection of papilla only	Adult distribution with spread to medial thigh		Cessation of growth at around 14–16 years	Adult genitalia	Ovarian volume: 2.5–5 cm³ Ut length: 5–15 cm Ut/Cx ratio: 3:1 Accrual of maximum BMD

Abbreviations: UT, uterine; Ut/Cx ratio, uterine fundus/cervical ratio; BMD, bone mineral density.

Table 3 Sexual maturity rating by Tanner's staging in boys and linear growth in puberty

Tanner stage	Genital development (G)	Pubic hair development (P)	Illustrations of G and P	Linear growth	Other changes
Stage 1	Prepubertal	Prepubertal vellus hair only	3 <2.5	Prepubertal rate: 5–6 cm per year.	Adrenarche
Stage 2	Testicular size ≥ 4 mL in volume or ≥ 2.5 cm in length Thinning and reddening of scrotal skin Early penile growth	Sparse growth at the base of penis	4 2.5–3.2	Prepubertal rate: 5–6 cm per year	Reduction in total body fat
Stage 3	Testicular size 10–15 mL in volume or ≥ 3.3–4 cm in length Growth of penis Scrotal thickening and pigmentation	Darker, coarser, curled hair: spreads to mons pubis	10 3.6	Accelerated growth: 7–8 cm per year	Gynecomastia Voice break Increase in muscle mass
Stage 4	Testicular size 15–20 mL in volume or ≥ 4–4.5 cm in length Penile growth in breadth and increase in glans size Darkening of scrotum	Adult pattern but without spread to medial thigh	16 4.1–4.5	Peak height velocity (PHV): 9–11 cm per year	Adult axillary hair (A) Voice change Acne
Stage 5	Adult genitalia Testicular size 25 mL in volume or > 4.5 cm in length	Adult distribution with spread to medial thigh	25 >4.5	Deceleration and cessation around 16–18 years	Facial hair Muscle mass increases further. Accrual of maximum bone mineral density

MORE ON THIS TOPIC

Buck Louis GM, Gray LE, Marcus M, et al. Environmental factors and puberty timing: expert panel research needs. Pediatrics. 2008;121:S192-207.

Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. Reproduction. 2010;140(3):399-410.

Ebling FJ. The neuroendocrine timing of puberty. Reproduction. 2005;129(6): 675-83.

Hughes IA. The testes: disorders of sexual differentiation and puberty in the male. In: Sperling MA. Pediatric Endocrinology, 3rd ed. Philadelphia: Saunders Elsevier; 2008. pp. 662-85.

Khadilkar V, Stanhope R. Secular trends in puberty. Indian Pediatr. 2006;43: 475-8.

Pinilla L, Aguilar E, Dieguez C, et al. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. Physiol Rev. 2012;92:1235-316.

Rosenfield RL, Cooke DW, Radovick S. Puberty and its disorders in the female. In: Sperling MA. Pediatric Endocrinology, 3rd ed. Philadelphia: Saunders Elsevier; 2008. pp. 530-609.

Seth A, Sharma R. Physiology of puberty. In: Desai MP, Menon PSN, Bhatia V. Pediatric Endocrine Disorders, 3rd ed. Hyderabad: Universities Press; 2014. pp. 123-31.

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1. Puberty is the stage of transition from sexually immature child to sexually mature and results from the awakening of a complex neuroendocrine mechanism.
2. GPR54, kisspeptin, leptin, optimal nutrition and epigenetic modulations such as by makorin ring finger protein 3 (MKRN3), besides others, are important factors in the regulation of puberty.
3. Onset of puberty correlates with bone age.
4. The first sign of puberty in girls is thelarche and in boys is increase in testicular volume to greater than or equal to 4 mL.
5. Adrenarche and gonadarche are independent processes.
6. Estradiol is responsible for epiphyseal fusion and cessation of linear growth in both boys and girls.

Chapter 44.11
Delayed Puberty
Vijaya Sarathi, Nalini S Shah

Delayed puberty is a common problem during the adolescent period. It is defined as the absence of testicular enlargement in boys or breast development in girls at an age that is 2–2.5 standard deviation (SD) later than the population mean (traditionally, the age of 14 years in boys and 13 years in girls). *Pubertal arrest*, which is defined as no progress in puberty over two years or failure to complete the puberty (menarche in girls and complete genital development in boys) within 5 years after the onset of puberty, is also included in the definition of pubertal delay. Development of pubic hair is usually not considered in the definition because pubarche may result from maturation of the adrenal glands (adrenarche), and the onset of pubic hair can be independent of hypothalamic-pituitary-gonadal (HPG) axis activation.

ETIOLOGY

The causes of delayed puberty are listed in **Table 1**. The common causes of delayed puberty are discussed in brief below and include constitutional delay in growth and puberty (CDGP), isolated hypogonadotropic hypogonadism (IHH) including Kallmann

syndrome, Klinefelter syndrome in boys and Turner syndrome in girls.

Constitutional Delay in Growth and Puberty

Constitutional delay in growth and puberty represents the single most common cause of delayed puberty in both boys and girls. It accounts for 65% boys and 30% girls with delayed puberty. CDGP occurs due to physiologic immaturity of HPG axis with a slow tempo of maturation; full sexual maturity will be reached, but the process takes longer than usual. The cause of CDGP is unknown, but it has a strong genetic basis; 50–75% of patients with CDGP have a family history of delayed puberty.

The growth rate before the actual onset of puberty in CDGP is often suboptimal for chronologic age, but growth velocity usually increases to normal levels after puberty begins. Affected boys are often more distressed by short stature than by delay in sexual development. Treatment with short course of sex steroids may be helpful to speed up the pubertal development and height spurt. Adult heights in CDGP are often slightly shorter than expected on the basis of parental heights.

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism may result from a genetic or developmental defect or it may be caused by a tumor, inflammatory process, vascular lesion, irradiation, or trauma to the hypothalamus. Similarly, hypogonadotropic hypogonadism

Table 1 Causes of delayed puberty

Constitutional delay in growth and puberty	
Hypergonadotropic hypogonadism	*Hypogonadotropic hypogonadism*
Males	*Isolated gonadotropin deficiency*
Klinefelter syndrome	Kallmann syndrome (mutations in *KAL1, FGR1, FGF8, PROK2, PROKR2, CHD7, NELF,* etc.)
Chemotherapy	Normosmic IHH (mutations in *GNRH1, GNRHR, KISS1, KISS1R, TAC3, TACR3, LEP, LEPR,* etc.)
Radiation therapy	Congenital adrenal hypoplasia (*DAX1* mutation)
Testicular steroid biosynthetic defects	Isolated LH or FSH deficiency
Sertoli-only syndrome	
LH receptor mutation	*Genetic forms of multiple pituitary hormone deficiencies*
Anorchia and cryptorchidism	Mutations in *PROP1, HESX1, LHX3, PHF6*
Trauma/surgery	
Orchitis	*CNS lesions*
	Tumors (craniopharyngiomas, germinomas, hypothalamic and optic gliomas, pituitary tumors, etc.)
Females	Langerhans' histiocytosis
Turner syndrome	Postinfectious lesions of the CNS (e.g., tuberculosis)
XX and XY gonadal dysgenesis	Vascular abnormalities of the CNS
Aromatase deficiency	Cranial irradiation
Radiation therapy	Head trauma
Chemotherapy	Lymphocytic hypophysitis
Autoimmune oophoritis	
Galactosemia	*Endocrinopathies*
Carbohydrate-deficient glycoprotein syndrome type 1	Hypothyroidism
Resistant ovary syndrome	Cushing disease
FSH receptor mutation	Hyperprolactinemia
Trauma/surgery	Diabetes mellitus
Noonan syndrome	
Ovarian steroid biosynthetic defects	*Miscellaneous disorders*
	Syndromes (Prader-Willi, Bardet-Biedl syndromes, etc.)
	Functional gonadotropin deficiency
	Chronic systemic disease and malnutrition
	Anorexia/bulimia nervosa
	Hypothalamic amenorrhea
	Marijuana use

may arise from lesions or defects that involve the pituitary gland directly.

Isolated Hypogonadotropic Hypogonadism

A defect involving the gonadotropin-releasing hormone (GnRH) pulse generator or gonadotropes without an anatomic lesion causes selective deficiency of gonadotropins, producing IHH. Prepubertal concentration of gonadal sex steroid values (testosterone in boys; estradiol in girls) and low or normal serum gonadotropin levels are characteristic. In boys, micropenis, undescended testes and gynecomastia are common findings in children with IHH.

Kallmann syndrome, the most common form of IHH is characterized by anosmia or hyposmia resulting from agenesis or hypoplasia of the olfactory lobes or sulci in association with GnRH deficiency. It is seen in 1 in 10,000 males and 1 in 50,000 females. Because affected individuals often do not notice impaired olfaction, testing with graded dilutions of pure scents is necessary. Mutations in *KAL1, FGFR1/FGF8, PROK2/PROKR2, NELF, CHD7, HS6ST1, WDR11,* and *SEMA3A* are associated with defects in neuronal migration, leading to Kallmann syndrome. It is most commonly inherited by X-linked recessive pattern (due to mutation in *KAL* gene that encodes anosmin) and less commonly by autosomal patterns. Defects in *FGFR1, FGF8, PROKR2, CHD7,* and *WDR11* have also been associated with normosmic IHH, although in a lower frequency. Associated defects that may accompany Kallmann syndrome include cleft lip, cleft palate, imperfect facial fusion, seizure disorders, short metacarpals, pes cavus, neurosensory hearing loss, cerebellar ataxia and nystagmus, ocular motor abnormalities, unilateral or rarely bilateral renal aplasia or dysplasia, and bimanual synkinesia (involuntary movement of muscles or limbs accompanying a voluntary movement). Mutations in *KISS1/KISS1R, TAC3/TACR3,* and *GNRH1/GNRHR* genes that interfere in the secretion and action of GnRH, are described exclusively in patients with normosmic IHH. Despite these great advances, the genetic basis of most cases of congenital IHH remains unknown, with the molecular basis of this condition being identified in approximately 30% of patients.

Klinefelter Syndrome

Klinefelter syndrome occurs in approximately 1 in 1,000 males, and is the most common form of male hypergonadotropic hypogonadism. It is associated with the characteristic karyotype of 47,XXY. Children with Klinefelter syndrome often enter puberty normally but will have pubertal arrest. The clinical features include small, firm testes, impaired spermatogenesis, long legs but not long arms and gynecomastia. Prepubertally, patients can be detected by the disproportionate length of the extremities. Neurobehavioral abnormalities, primarily in language, speech, learning, and frontal executive functions, are common. Conditions associated with Klinefelter syndrome include aortic valvular disease, ruptured berry aneurysms, breast carcinoma and other malignancies such as acute leukemia, lymphoma, and germ cell tumors at any midline site; systemic lupus erythematosus; and osteoporosis. There is an increased risk of diabetes mellitus, thyroid disease, fatigue, varicose veins, and essential tremor.

Turner Syndrome

It is the most common form of hypergonadotropic hypogonadism in females. It is the syndrome of gonadal dysgenesis, a sporadic disorder with an incidence of 1 per 2,500 live-born girls in which all or part of the second sex chromosome is absent.

Turner syndrome may be recognized in the newborn period. Affected newborn infants may have cystic hygroma in the neck and lymphedema of the extremities. Other frequent features are short stature, distinct facies with micrognathia, a fish-mouth appearance, high-arched palate with dental abnormalities, epicanthic folds, ptosis, low-set or deformed ears, short neck with low hairline, webbed neck, and recurrent otitis media, often leading to impaired hearing. A broad, shield like chest leads to the appearance of widely spaced nipples, and the areolae are often hypoplastic. Skeletal defects include short fourth metacarpals and cubitus valgus (which may develop after birth), Madelung deformity of the wrist, genu valgum, and scoliosis. There may be extensive pigmented nevi, a tendency to keloid formation, and hypoplastic nails. Cardiovascular anomalies affect the left side of the heart and include coarctation of the aorta, aortic stenosis, and bicuspid aortic valves; the latter individuals are at risk for a dissecting aortic aneurysm. Details of Turner syndrome are provided in Chapter 2.4.

DIAGNOSIS

History and Physical Examination

A detailed history should be obtained regarding the growth pattern of the child since birth and pubertal development. It is important to know whether puberty failed to occur, or it began but failed to progress or even regressed. Particular emphasis should be given to elicit the history of anosmia or hyposmia, cryptorchidism and micropenis, which are closely associated with hypogonadotropic hypogonadism. The history to elicit the risk factors for hypogonadism should include exposure to chemotherapy or radiotherapy, brain tumors, neuroinfections, head injury, etc. In addition, a detailed history should be taken to rule out any chronic or intermittent systemic illnesses that can delay the onset of puberty (functional hypogonadotropic hypogonadism), as well as medication use, nutritional status, and psychosocial functioning. Delayed cognitive development associated with obesity or dysmorphic features may suggest an underlying genetic syndrome.

A family history, including childhood growth patterns and age at pubertal onset of the parents, should be obtained. Recalled age of pubertal onset is relatively reliable in women but less often accurate in men. Delayed puberty in a parent or sibling followed by spontaneous onset of puberty suggests CDGP. All etiologies of IHH may be reversible spontaneously.

The physical examination should include determination of height, weight, upper-to-lower segment ratio and the arm span-height difference. Eunuchoid proportions (long lower segment) strongly suggest hypogonadism. A growth chart is plotted to represent graphically the increase in stature and to assess growth velocity from birth. The height velocity should be documented over a period of at least 6 months, preferably 12 months. Constitutionally delayed puberty is often associated with short stature and slow growth for age although the height and growth rate are within the prepubertal normal range. Late-onset growth failure usually indicates a serious condition requiring immediate evaluation. Weight is plotted to determine states of malnutrition. Children who are underweight for height have an increased likelihood of having an underlying condition delaying HPG axis activation. The signs of puberty are assessed, and the stage of secondary sexual development is determined by physical examination according to the Tanner staging. In boys, the presence of Tanner stage 2 genitalia marks the onset of pubertal development and is characterized by enlargement of the scrotum and testes and by a change in the texture and color of the scrotal skin. Testicular volume should be measured, with a volume of more than 3 mL indicating the initiation of central puberty. Examination should include tests for anosmia with graded solutions of pure scents or standard smell test kits.

Investigations

An algorithmic approach to a child with delayed puberty is depicted in **Flow chart 1**. Bone age should be assessed by comparing X-ray of left hand and wrist with standard photographs (Greulich and Pyle atlas). A moderate delay in bone age is characteristic of CDGP although bone age delay may also be seen in hypogonadism, functional hypogonadotropic hypogonadism and endocrinopathies.

First-line hormonal evaluation should include serum 8:00 am total testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Thyroid function tests are routinely done. Insulin-like growth factor-1 (IGF-1) levels may be done, especially if bone age is markedly delayed. Raised FSH and LH suggest hypergonadotropic hypogonadism (primary gonadal failure). A karyotype should be done in these individuals, mainly to rule out Klinefelter syndrome in boys and Turner syndrome in girls. Gonadotropins will be low or normal in CDGP, IHH, other endocrinopathies and functional hypogonadotropic hypogonadism. The screening tests to rule out causes of functional hypogonadotropic hypogonadism should include complete hemogram, erythrocyte sedimentation rate, renal and liver function tests, serum electrolytes including bicarbonate, serum calcium, and phosphorus and screening for celiac disease in high risk groups.

Although CDGP represents the single most common cause of delayed puberty in both sexes, it can be diagnosed only after underlying conditions have been ruled out. After ruling out functional hypogonadotropic hypogonadism and primary hypothyroidism with clinical and biochemical evaluation, the task is to differentiate CDGP from IHH, which is highly challenging. A serum total testosterone value of more than 50 ng/dL, a GnRH agonist (triptorelin) stimulated peak LH value of more than 14 IU/L and a human chorionic gonadotropin (hCG) stimulated increase in total testosterone of more than 260 ng/dL predict CDGP with 100% positive predictive value. However, the values below these values do not predict IHH accurately. Serum inhibin B has recently been found as a useful test to distinguish CDGP from IHH and a value greater than 35 pg/mL is highly suggestive of CDGP. However, none of these appear to be a practical and reliable endocrine test for indisputably differentiating CDGP and IHH. Watchful waiting remains the procedure of choice when a patient does not fulfill the delineated criteria.

MANAGEMENT

For psychological reasons, in boys aged more than 14 years and girls aged more than 13 years with CDGP and no signs of puberty,

Flow chart 1 An algorithmic approach to an adolescent with delayed puberty
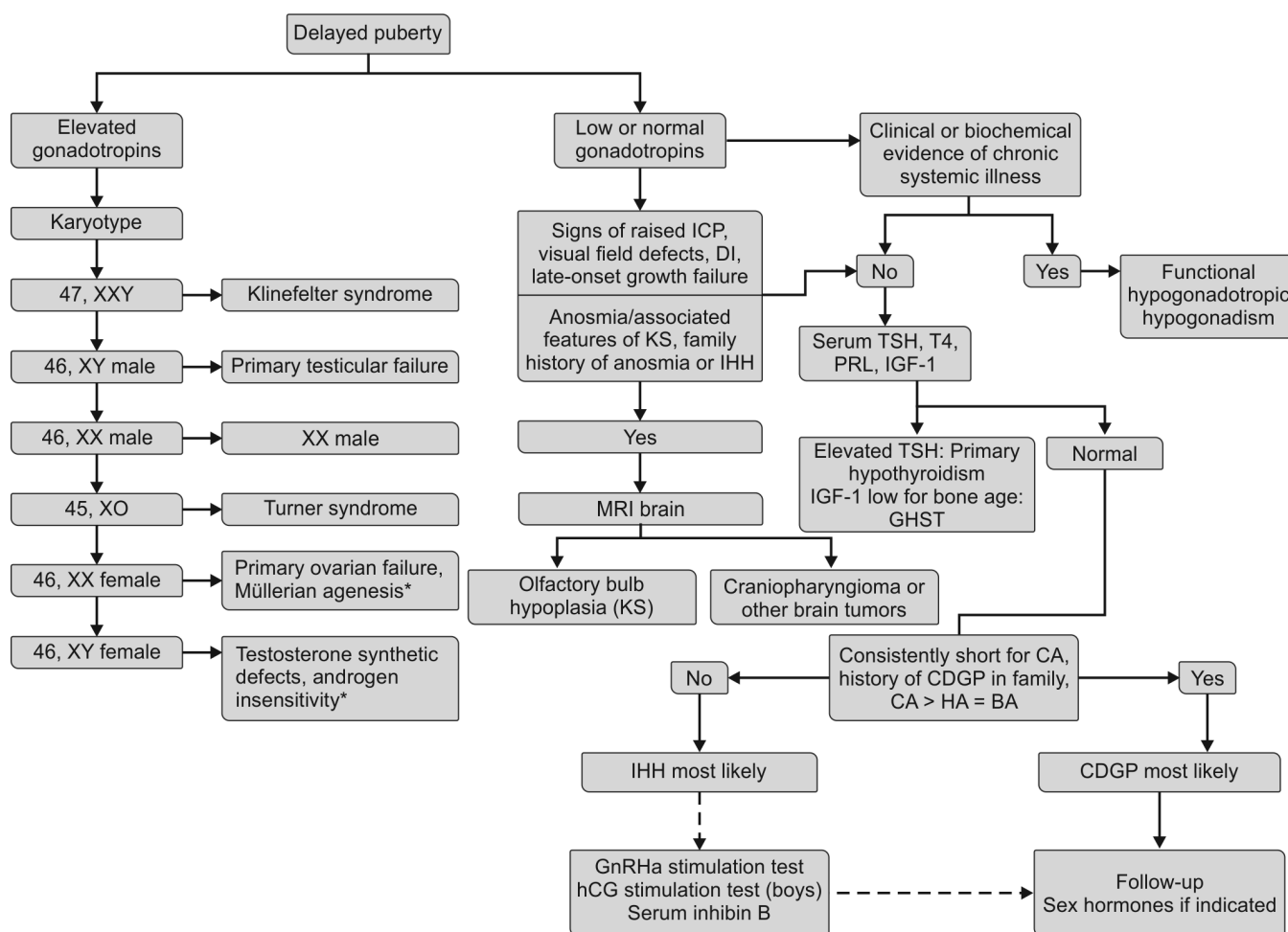
*Normal breast development with amenorrhea

Abbreviations: BA, bone age; CA, chronological age; CDGP, constitutional delay in growth and puberty; DI, diabetes insipidus; GHST, growth hormone stimulation test; GnRHa test, gonadotropin-releasing hormone analog stimulation test; HA, height age; hCG test, human chorionic gonadotropin stimulation test; ICP, intracranial pressure; IHH, isolated hypogonadotropic hypogonadism; IGF-1, insulin-like growth factor 1; KS, Kallmann syndrome; PRL, prolactin; TSH, thyroid-stimulating hormone; T4, thyroxine.

a 3–6-month course of sex steroid therapy may be helpful. Boys are commonly treated with testosterone enanthate (50–100 mg given intramuscularly every 4 weeks), and girls with ethinyl estradiol (5 μg/day PO) or conjugated estrogens (0.3 mg/day PO). Therapy should be withheld for next 4-6 months and pubertal status should be reevaluated including serum testosterone or estradiol. If indicated repeat treatment may be given for another 3–6-month period. When treatment is discontinued, patients with CDGP usually continue pubertal development on their own, whereas those with IHH do not progress and may regress.

Functional hypogonadotropic hypogonadism associated with chronic disease is treated by alleviating the underlying problem. Treatment with levothyroxine allows normal pubertal development in hypothyroid patients with delayed puberty.

Permanent hypogonadism of any cause requires lifelong therapy. In established cases of permanent hypogonadism, treatment with sex steroids should begin at the age of 12–13 years in girls and 13–14 years in boys. Induction of puberty should be gradual. Boys should be treated initially with 50 mg of intramuscular testosterone enanthate (or other long-acting testosterone ester) every month for about 9 months (6–12 months). Over the next 3–4 years, the dose is gradually increased to adult replacement dose of 200 mg once in 2–3 weeks. Initial therapy of girls should be with estradiol valerate 0.25–0.5 mg, conjugated estrogen 0.1625–0.325 mg or ethinyl estradiol 2.5–5 μg by mouth daily for 6 months and dose of estrogen gradually increased over next 2–3 years to estradiol valerate 2 mg, conjugated estrogen 0.6–1.25 mg or ethinyl estradiol 10–20 μg daily. After 12–18 months of therapy (or sooner if breakthrough bleeding occurs), cyclic therapy should be started with estrogen during first 21 days of month and progestogen (medroxyprogesterone acetate 5 mg PO) 12th to 21st day of month. Recently, transdermal preparations are becoming popular. Whenever fertility is desired in patients with hypogonadotropic hypogonadism, treatment with pulsatile GnRH or FSH and hCG therapy may be warranted.

IN A NUTSHELL

1. Delayed puberty is defined as the absence of testicular enlargement in boys by the age of 14 years or breast development in girls by age 13 years. Pubertal arrest is suspected when puberty has not completed by 5 years from its onset.
2. Constitutional delay of growth and puberty, a spontaneously resolving physiological condition, is the most common cause of delayed puberty.
3. Kallmann syndrome is the prototype example of hypogonadotropic hypogonadism. Several other genetic mutations have also been elucidated. Hyperprolactinemia and other pituitary-hypothalamus lesions must be looked for.
4. Klinefelter syndrome is the prototype example of hypergonadotropic hypogonadism. Primary testicular failure is also caused by infection, chemotherapy, and radiation damage, among others.
5. Induction of puberty by gonadal steroids is brought about by slowly escalating doses to mimic normal puberty.

MORE ON THIS TOPIC

Fenichel P. Delayed puberty. Endocr Dev. 2012;22:138-59.
Gonzalez L, Witchel SF. The patient with Turner syndrome: puberty and medical management concerns. Fertil Steril. 2012;98(4):780-6.
Kaplowitz PB. Delayed puberty. Pediatr Rev. 2010;31(5):189-95.
Palmert MR, Dunkel L. Clinical practice: Delayed puberty. N Engl J Med. 2012;366(5):443-53.
Silveira LF, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2013;98(5):1781-8.
Watson S, Fuqua JS, Lee PA. Treatment of hypogonadism in males. Pediatr Endocrinol Rev. 2014;11 Suppl 2:230-9.

Chapter 44.12
Precocious Puberty
Prisca Colaco

The timing of puberty is influenced by both genetic and environmental factors. Precocious puberty has been defined as the onset of puberty occurring earlier than the norms for gender and race or ethnic background. Traditionally, puberty was considered precocious if its onset occurred before 8 years in girls and 9 years in boys. As several studies in the US in the 1990s found that puberty is being achieved about a year earlier in white girls and 2 years earlier in African-American girls, it was recommended that puberty be considered precocious when breast development or pubic hair appears before the age of 7 years in white girls and 6 years in black girls. However, as some girls between 6 and 8 years of age were found to have significant underlying pathology, the earlier cutoff of 8 years in girls is most often followed. For boys, the onset of puberty before the age of 9 years is considered precocious.

CLASSIFICATION

Sexual precocity can be classified as:
- Central precocious puberty (CPP) or true or gonadotropin-dependent precocious puberty
- Peripheral precocious puberty (PPP) or pseudo- or gonadotropin-independent precocious puberty
- *Incomplete forms or pubertal variants*: Premature thelarche (PT), premature adrenarche and premature menarche.

CENTRAL PRECOCIOUS PUBERTY

Central precocious puberty is due to the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis and is the most common form of precocious puberty. It is about five times more common in girls than in boys. Pubertal development is always isosexual. The causes **(Table 1)** are similar in boys and girls. CPP may be neurogenic but in 75–90% of girls, it is idiopathic. Underlying central nervous system (CNS) pathology is found in about two-third of the boys. The younger the child, the greater is the likelihood of underlying pathology. In idiopathic CPP, the appearance of sexual characteristics is merely a normal event occurring early and puberty progresses normally. A familial tendency to early puberty may be observed in some cases. Internationally adopted children appear to be at increased risk for CPP. The reason for this is unclear.

Hypothalamic hamartomas are the most common tumors causing precocious puberty **(Fig. 1)**. These consist of heterotopic CNS tissue which contain gonadotropin-releasing hormone (GnRH) secreting neurons and act as ectopic GnRH pulse generators. Puberty may occur at a very early age, is rapidly progressive and is often associated with gelastic or other types of seizures and developmental delay. Serum luteinizing hormone (LH) levels and response to GnRH stimulation are very high.

Cranial irradiation in low or moderate doses can result in precocious puberty. In India, infections of the CNS, particularly tuberculous meningitis, are important causes of neurogenic CPP. CPP may be transient in some cases where the pathology is treatable, e.g., hydrocephalus and granulomas. CNS lesions may be associated with concomitant GH deficiency which may be masked by sex steroid driven adequate growth rates. In such cases, undiagnosed untreated GH deficiency can result in severely compromised adult height.

Long-term exposure to sex steroids due to gonadotropin-independent processes may result in early central puberty,

Table 1 Causes of central precocious puberty

GnRH-dependent: Both boys and girls
• Idiopathic
• International adoption
• Neurogenic
– Acquired CNS insults:
- *Trauma, perinatal insult*
- *Postinfection (meningitis or encephalitis)*
- *CNS granulomatous disease*
- *Iatrogenic: Low-dose cranial irradiation, chemotherapy, surgery*
– Tumors:
- *Hypothalamic hamartoma*
- *Astrocytoma*
- *Pineal tumor*
- *Ependymoma*
- *Glioma (optic pathway)*
- *Craniopharyngioma (rare)*
– Structural defects
- *Hydrocephalus*
- *Subarachnoid cyst*
- *Septo-optic dysplasia (rare)*
– Phakomatoses
- *Neurofibromatosis type 1*
- *Tuberous sclerosis*
– Other pathologies
- *Cerebral palsy*
• Withdrawal of chronic sex hormone exposure
• Genetic: Gain of function mutation of kisspeptin/kisspeptin receptor
• Prolonged undertreated peripheral precocious puberty
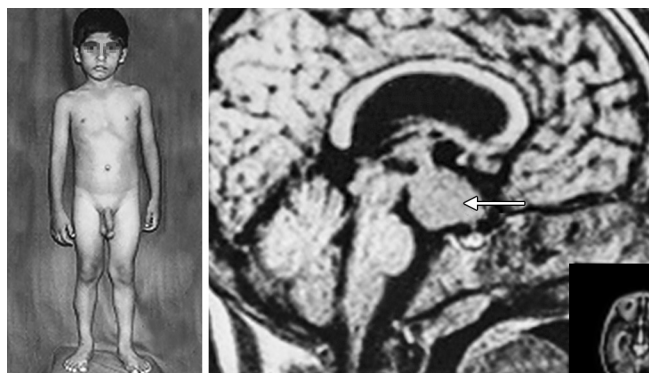
Figure 1 A 3-year-old boy with CPP due to a hypothalamic hamartoma. Note enlargement of the external genitalia, especially the testes along with the generally muscular physical appearance. The white arrow indicates the hypothalamic hamartoma in the MRI of brain

generally when the bone age reaches 10–13 years. This usually occurs after removal of the cause of peripheral puberty.

PERIPHERAL PRECOCIOUS PUBERTY

Peripheral precocious puberty results from the production of sex steroids independent of HPG axis. The etiology is shown in **Table 2**. It may be due to adrenal or gonadal causes. PPP is only about one-fifth as common as CPP. The sequence of pubertal changes is usually discordant, i.e., in boys, unlike the normal progression from testicular enlargement to the development of the external genitalia and the appearance of pubic hair, the genitalia may appear mature while the testes remain underdeveloped, or in girls breast development may progress without the appearance of pubic hair. Unlike CPP, the etiologies of PPP differ in the two genders **(Table 2)** and may result in heterosexual development.

Table 2 Causes of isosexual peripheral precocious puberty

GnRH-independent in girls	GnRH-independent in boys
Ovarian disorders: • *Ovarian cyst* • *Hyperplasia* McCune-Albright syndrome *Estrogen-secreting tumors*: • *Ovarian (granulosa-theca cell tumor, gonadoblastoma, teratoma)* • *Adrenal* Exogenous estrogen exposure Peutz-Jegher syndrome (ovarian sex cord tumors) Primary hypothyroidism Aromatase excess	*Adrenal disorders*: • Congenital adrenal hyperplasia • Tumors Familial male-limited precocious puberty (testotoxicosis) *Testosterone-secreting tumors*: • Leydig cell • Adrenal rests *hCG-secreting tumors*: • Hepatoblastoma • Pineal gland tumors • Cerebral tumors (germinoma) • Mediastinal tumors • Gonadal tumors Exogenous androgen (testosterone) exposure Primary hypothyroidism (testicular enlargement only) Familial glucocorticoid resistance McCune-Albright syndrome (rare)

Adrenal disorders, most commonly congenital adrenal hyperplasia (CAH), are the most common causes of isosexual peripheral precocity in males. Peripheral precocious puberty is therefore much more common in boys as compared to girls. The prepubertal size of the testes suggests the diagnosis.

Familial male-limited precocious puberty (FMPP) or testotoxicosis is a rare autosomal dominant disorder due to an activating mutation of the LH receptor. The onset is at 2–3 years of age. Pubertal development is considerable and includes symmetrical enlargement of the testes which is however disproportionately small for the degree of virilization.

hCG-secreting tumors such as hepatoblastoma or tumors arising from the pineal gland, cerebrum, mediastinum and gonads also cause precocious puberty in boys. Testicular size is slightly increased and testosterone levels are elevated. Leydig cell tumors cause unilateral enlargement of the testes.

Ovarian rather than adrenal disorders are much more likely in girls with PPP. The most common are autonomous secreting follicular cysts of the ovary. These cysts are often more than 2 cm in diameter in contrast to the smaller cysts which may be normally present in the prepubertal ovary or in CPP. Pubertal signs often develop rapidly. Subsequent atresia of the cysts results in withdrawal bleeding.

McCune-Albright syndrome (MAS) consists of the triad of fibrous bony dysplasia, skin pigmentation and precocious puberty, and predominantly affects girls **(Fig. 2)**. It occurs due to the mutation that activates the gene encoding Gs protein-α subunit. It may have incomplete forms and may be the cause of recurrent follicular cysts and irregular vaginal bleeding even without other signs.

Hypothyroidism, untreated or inadequately treated, is sometimes associated with breast development, vaginal bleeding, and cystic ovaries in girls and bilateral testicular enlargement in boys referred to as the Van Wyk Grumbach syndrome **(Fig. 3)**. The cause is not clear but it is thought to be due to the effect of markedly elevated TSH levels on the follicle-stimulating hormone (FSH) receptor. It is not associated with pubarche or acceleration in growth and skeletal maturation. Increase in prolactin levels and galactorrhea may accompany the pubertal signs. The treatment of hypothyroidism causes recovery.

Heterosexual PPP in girls may be due to CAH or virilizing adrenal or ovarian tumors and in boys feminizing tumors of the testis or adrenal.

Figure 2 A 7-year-old girl with McCune-Albright syndrome. Note the premature thelarche and the café-au-lait macules on the chest

Figure 3 A 6-year-old boy with hypothyroidism and bilateral testicular enlargement

PUBERTAL VARIANTS

The incomplete forms of sexual precocity can be differentiated from precocious puberty by the absence of other signs of puberty and a normal growth rate.

Premature Thelarche

Premature thelarche is defined as isolated breast enlargement in girls without any additional signs of pubertal development. It may be unilateral or bilateral. Breast development usually occurs before 2 years of age and rarely after 4 years. It generally regresses within 18 months but complete regression may not be seen in those whose onset was after 2 years of age or with Tanner stage 3. Areolar development, as seen in normal puberty, is absent. There is no other evidence of estrogen effects such as changes in vaginal mucosa, increase in uterine size, rapid progression of breast size, growth acceleration or bone age advancement. It is thought to be due to increased sensitivity of breast tissue to low levels of circulating estrogen. Girls with premature thelarche go on to have normal puberty and normal fertility and attain a normal final adult height. Exogenous estrogens in food or environmental exposure could also lead to premature breast development.

Premature thelarche which starts after 2 years of age may progress to CPP and is known as *thelarche variant* or *slowly progressive precocious puberty*. Breast enlargement in these children may slowly increase together with an increase in growth rate and skeletal maturation or in some may show cyclical changes in size.

Premature Pubarche

Premature pubarche refers to the appearance of pubic and/or axillary hair before the age of 8 years in girls and 9 years in boys. It is a consequence of premature adrenarche—increased production of adrenal androgens. It is more commonly seen in girls in the 6–8-year age group and in obese children. Pubarche is not progressive. Occasionally, these children may develop slight acne, axillary hair, and adult type body odor but no other secondary sexual characteristics. Skeletal maturation and linear growth are at upper normal limits. The onset and progression of puberty and eventual height are normal in these children. An increase in androgen receptor gene activity has been found in some cases of premature pubarche. Signs of severe androgen excess such as clitoromegaly, increased muscle mass, deepening of the voice or hirsutism should prompt a search for a virilizing condition such as an adrenal tumor or CAH. Premature pubarche has been associated with intrauterine growth retardation and the later development of polycystic ovaries and the metabolic syndrome.

Premature Menarche

Premature menarche is a term used for vaginal bleeding which occurs in isolation without other signs of puberty at an unusually early age. Growth and skeletal maturation are normal and the uterus is prepubertal on ultrasound. It is a very rare condition of unclear etiology. Other causes of bleeding must be investigated and excluded.

EVALUATION

A diagnostic evaluation is important to determine the etiology so that appropriate treatment may be given **(Table 3)**.

Clinical Evaluation

The history should note the age at onset of puberty, the pattern of growth and rapidity of progression of puberty, past CNS infections and symptoms of CNS disease, exposure to exogenous hormones and birth details and family history of early puberty.

Idiopathic CPP usually presents around 6–7 years of age and may sometimes be very slowly progressive with menarche occurring 4–5 years after the onset of breast development. A very early onset, in the first 3–4 years and rapid progression suggests the possibility of a hypothalamic hamartoma or familial testotoxicosis. Very rapid progression of puberty is also seen in androgen-producing tumors and ovarian cysts. Irregular vaginal bleeding is more common in functioning ovarian tumors and hypothalamic hamartoma. Pointers to a neurologic disorder are a history of past CNS infection, headaches, visual disturbances, personality changes, developmental delay and seizures.

A family history of precocious puberty would suggest constitutional precocious puberty and a similar pattern of early development in males in the family suggests familial testotoxicosis. A history of precocious puberty in boys and genital ambiguity in girls of the same family is typical of CAH.

Examination must include anthropometry with serial height measurements, staging of puberty according to the Tanner method and testicular palpation. A testicular volume of more than 3 mL indicates the onset of CPP. Scrotal masses suggest testicular tumors or adrenal rests. Androgen and estrogen effects must be evaluated. Androgen effects include acne, hirsutism, increased muscle mass and clitoromegaly. Estrogen effects include breast development and vaginal mucosal changes. In obese girls, lipomastia needs to be differentiated from breast enlargement. On palpation absence of tissue in the subareolar region, *doughnut sign*, helps to recognize breast tissue or sonography may be helpful. Inspection of the skin is helpful in MAS, neurofibromatosis and tuberous sclerosis. Examination should include palpation of the thyroid and a search for evidence of hypothyroidism, abdominal examination for any mass and neurologic examination including fundoscopy.

Investigations

Hormonal Evaluation

The first step in the hormonal evaluation is a measurement of gonadotropin levels—LH, FSH and gonadal hormones—and estradiol/testosterone, followed by a GnRH stimulation test.

Gonadotropin levels are elevated in CPP and suppressed in PPP. With the availability of sensitive third-generation assays (immunochemiluminometric assay or ICMA), random LH is a good screening test for CPP. An LH level of less than 0.1 IU/L is prepubertal and 0.3 IU/L or more is pubertal. Random FSH levels are not helpful in discriminating between prepubertal and pubertal children.

Table 3 Differential diagnosis of precocious puberty

	Sequence of pubertal changes	*Growth*	*BA*	*Gonadal hormones*	*Gonadotropins*	*GnRH stimulation*
CPP	Concordant	+	+	↑	↑ LH	LH predominant
PPP	Discordant	+	+	↑	Suppressed	No rise
PT	No progression	N	N	Prepubertal	Prepubertal	FSH predominant
PA	No progression	N	N	Prepubertal	Prepubertal	Prepubertal

Abbreviations: BA, bone age; FSH, follicle stimulating hormone; LH, luteinizing hormone; CPP, central precocious puberty; PPP, peripheral precocious puberty; PT, premature thelarche; PA, premature adrenarche; N, normal for age; +, advanced; ↑, elevated.

Gonadotropin stimulation with either GnRH or GnRH analog, provides the best evidence of gonadarche predominantly using the LH response. It is also more helpful in distinguishing central from peripheral precocity. Normal prepubertal children have an increment of 3–4 IU/L of LH and 2–3 IU/L of FSH levels following stimulation. In CPP, an LH predominant response is seen with GnRH stimulation. FSH levels, both basal and peak, have poor diagnostic value in CPP. After stimulation, peak LH levels of greater than 5–8 IU/L using ICMA, are considered to be diagnostic for CPP in children between 2 and 8 years. Cutoff values differ depending on the assay used to measure LH. LH/FSH ratio is greater than 1 after the onset of puberty, but has lower sensitivity and specificity in comparison to the peak LH level in the diagnosis of CPP. In PPP, gonadotropin levels are suppressed by gonadal hormones and do not rise in response to GnRH stimulation. The response to GnRH is prepubertal in premature adrenarche; FSH predominant in premature thelarche and intermediate between premature thelarche and CPP with FSH predominating in thelarche variant.

Sex steroids In girls, serum estradiol levels are not very helpful. Levels overlap between normal prepuberty, early puberty, precocious puberty and premature thelarche. Levels greater than 20 pg/mL suggest that puberty has started. Markedly elevated levels greater than 100 pg/mL are seen in estrogen-secreting ovarian tumors and sometimes in follicular cysts.

Serum testosterone In boys, serum testosterone levels less than 30 ng/mL are generally prepubertal, though in some laboratories levels of 10–30 ng/mL may indicate early puberty. Basal plasma testosterone levels are elevated in both CPP and PPP, but are much higher in PPP patients.

Serum dehydroepiandrosterone sulfate (DHEAS) levels are in the pubertal range in premature adrenarche (> 40 µg/dL) and can be very high in virilizing adrenal disorders.

Serum 17-hydroxyprogesterone (17OHP) and the response to ACTH or serum 11-deoxycortisol may be required to rule out CAH.

Serum hCG levels must be estimated if an hCG-secreting tumor is suspected in boys with precocious puberty.

Thyroid function studies are indicated in suspected hypothyroidism.

Imaging Studies

Bone age should be determined from an X-ray of the left hand and wrist. Acceleration of growth and skeletal maturation occurs in both CPP and PPP and can lead to compromised adult height but this is not seen in pubertal variants. Skeletal maturation is delayed if precocious puberty is associated with hypothyroidism. Bone age evaluation also helps to track the progression and assess the growth potential. Δ bone age/Δ chronological age ratio greater than 1.2 favors progressive CPP.

Computed tomography (CT) or MRI of brain to determine the etiology of CPP is indicated in all boys with CPP because of the high likelihood of underlying pathology. In girls, it may be necessary only in those below 6 years of age or in the presence of neurologic signs or rapid progression of puberty.

Computed tomography or MRI of the adrenals is indicated if there is a suspicion of an adrenal tumor.

Pelvic and abdominal sonography to evaluate the size and morphology of the uterus, ovaries and adrenals is essential in PPP to find the cause. The uterus is considered to be pubertal when there is a change from its prepubertal tubular shape to a pear-shaped structure where the size of the body is more than the cervix, the length increases to greater than 3.4 (range 3.4–4 cm) or volume to greater than 2 mL and an endometrial shadow is seen. The ovaries will be symmetrically increased in volume (cutoff ranges from 1 mL to 3 mL) and show multiple small follicular cysts. The shape of the uterus remains prepubertal in premature thelarche and thelarche variant. Ovarian asymmetry is classically seen in PPP due to autonomously functioning ovarian cysts.

Testicular sonography can detect nonpalpable Leydig cell tumors in cases of asymmetric testicular volume or PPP.

Bone scan and skeletal survey are indicated in suspected cases of MAS.

MANAGEMENT

The normal variants—premature pubarche, thelarche and thelarche variant do not need treatment. Any identified underlying pathology in CPP or PPP should be treated.

Management of Central Precocious Puberty

Treatment of CPP is indicated if:

- There is evidence that adult height may be significantly compromised
- Menarche occurs before 6 years of age
- Pubertal development is psychologically distressing to the child, and
- Pubertal development progresses rapidly over an observation period of about 6 months.

Therapy aims at reversing the development of sexual characteristics, and decreasing the acceleration of growth and bone age by using GnRH analog therapy. Long-acting GnRH analogs (GnRHa) produces continual exposure of the GnRH receptors on the pituitary gonadotropes to GnRH and results in downregulation of the receptors and decreased LH and FSH secretion. A variety of GnRHa formulations is available and efficacious **(Table 4)**. The depot intramuscular preparations are more effective than the intranasal formulations which require multiple dosing. The formulations available are extended depot leuprolide acetate—a 3 monthly

Table 4 Gonadotropin-releasing hormone agonists

Formulations	*Starting dose*
Depot GnRHa formulations	
Leuprolide	3.75 mg every month or 11.25 mg every 3 months SC or IM (0.2–0.3 mg/kg per month)
Triptorelin	3 or 3.75 mg every month or 11.25 mg every 3 months IM
Goserelin	3.6 mg every month or 10.8 mg every 3 months SC
Buserelin	6.3 mg every 2 months
Histrelin LA	50 mg implant every year (SC implant)
Rapid-acting GnRHa formulations	
Buserelin, deslorelin, histrelin, leuprorelin, leuprolide, nafarelin, triptorelin	Nasal spray or SC injection 1–3 times a day

Abbreviations: IM, intramuscular; SC, subcutaneous; GnRHa, GnRH analogs.

formulation of 11.25 mg leuprolide and 50 mg histrelin acetate implant which provides sustained suppression for 12 months.

At the initiation of therapy, there can be exacerbation in signs which may result in vaginal bleeding in girls due to the short-term stimulatory effect of GnRHa. With effective suppression, pubertal signs do not progress and may regress, growth rates decrease to prepubertal levels and skeletal maturation slows so that predicted adult height (PAH) increases. Adequate GnRHa therapy is evidenced by a suppressed random LH level using ultrasensitive assays or an absent response to GnRH stimulation, but clinical monitoring of pubertal signs, growth velocity, skeletal maturation and ultrasonographic findings may suffice.

Height loss due to precocious puberty is inversely correlated to the age at onset. Girls with onset of progressive CPP before 6 years of age benefit most in terms of height from GnRHa therapy (average gain 9–10 cm). Some between 6 and 8 years, with very rapid or advanced puberty may benefit, although many have a slowly progressive form which has a normal height outcome without treatment. There appears to be little benefit in terms of height in treating girls over the age of 8 years. Increase in PAH is better for boys than for girls. Treatment should be considered for all boys with onset of progressive CPP before 9 years of age who have compromised height potential.

Treatment should be stopped when the child reaches an age when the onset of puberty is acceptable. Gonadotropin secretion recommences within 4 months of cessation of therapy and most girls begin to menstruate about a year after stopping therapy.

On the basis of presently available data and potential adverse effects, the addition of GH or oxandrolone to GnRHa to improve adult height is not routinely recommended.

Potential new therapeutic agents for the treatment of CPP are *GnRH antagonists*. They cause immediate and direct inhibition at the level of pituitary GnRH receptors and have the theoretical advantage over GnRHa of eliminating the initial *flare* in gonadotropic axis activation and rapid recovery of suppression once therapy is withdrawn.

Antigonadotropic and antiandrogen drugs such as medroxy-progesterone and cyproterone acetate cause a regression of pubertal signs and suppress menstruation, but have no effect on growth acceleration and bone age progression.

Management of Peripheral Precocious Puberty

Treatment of FMPP using androgen receptor blockade and aromatase inhibition to limit clinical signs of androgen excess and excessive skeletal maturation with spironolactone and testolactone is effective, but requires multiple daily dosing. The newer androgen receptor antagonist bicalutamide along with the third-generation aromatase inhibitor, anastrazole is effective with once daily dosing.

Treatment of girls with MAS aims at inhibiting estrogen production or blocking its action. Aromatase inhibition with testolactone or partial estrogen receptor blockade with tamoxifen have not been adequately effective and have questionable long-term safety as their use has been associated with increased ovarian or uterine size. The third-generation aromatase inhibitor, letrazole appears to be effective and safer. Medroxyprogesterone acetate has been used with variable success but may exacerbate the bone lesions because of its hypocalcemic effect. A recent clinical trial of fulvestrant, a pure estrogen receptor blocker, has shown promising results.

In PPP, progression to CPP is common, and addition of GnRHa is often required.

Surgery

Tumors of the ovary, testis and adrenals require surgical removal. Ovarian cysts more than 3 cm in size should be explored surgically. Smaller cysts require repeated evaluation. Surgery of hypothalamic hamartoma is hazardous and is not recommended, because they do not grow or become malignant. Other CNS tumors can be surgically resected or given radiotherapy.

Psychological Support

Psychological support for the child and parents is an essential part of the general management scheme. No major psychopathology is associated with precocious puberty. Future fertility is maintained. There is a lack of adequate evidence of the effect of GnRHa therapy on quality of life and psychosocial functioning.

IN A NUTSHELL

1. Puberty is considered precocious, if its onset occurs before 8 years in girls and 9 years in boys.
2. Central precocious puberty is due to the premature activation of the HPG axis and is the most common form of precocious puberty, isosexual and more common in girls.
3. The younger the child, the greater is the likelihood of underlying pathology.
4. Hypothalamic hamartoma is the most common tumor causing precocious puberty.
5. Peripheral precocious puberty results from the production of sex steroids independent of HPG axis.
6. Gonadotropin levels are elevated in CPP and suppressed in PPP, and gonadotropin stimulation with GnRH or GnRH analog provides the best evidence of gonadarche.
7. Long-acting GnRH analogs are the preferred mode of treatment for CPP. Management of PPP is in general unsatisfactory.

MORE ON THIS TOPIC

Brook CGD, Brown RS. Problems of puberty and adolescence. Handbook of Clinical Pediatric Endocrinology. 1st ed. Massachusetts: Blackwell Publishing; 2008. pp. 59-83.

Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123:e752-62.

Carel JC, Léger J. Clinical practice: precocious puberty. N Engl J Med. 2008;358:2366-77.

Fuqua JS. Treatment and outcomes of precocious puberty: an update. J Clin Endocrinol Metab. 2013;98:2198-207.

Kakarla N, Bradshaw KD. Disorders of pubertal development: precocious puberty. Semin Reprod Med. 2003;21:339-51.

Lee PA, Kerrigan JR. Precocious puberty. In: Pescovitz OH, Eugster EA. Pediatric Endocrinology: Mechanisms, Manifestations, and Management. USA: Lippincott Williams & Wilkins; 2004. pp. 316-31.

Muir A. Precocious puberty. Pediatr Rev. 2006;27(10):373 -81.

Nebesio TD, Eugster EA. Current concepts in normal and abnormal puberty. Curr Probl Pediatr Adolesc Health Care. 2007;37:50-72.

Wales JK. Disordered pubertal development. Arch Dis Child Educ Pract Ed. 2012;97:9-16.

Chapter 44.13
Gynecomastia
Anju Virmani

Asymptomatic gynecomastia is a physiological finding in the vast majority of newborns, adolescents and elderly men. Defined as the presence of glandular breast tissue greater than 1 cm in males, it can range in appearance from tiny, perhaps tender, subareolar breast buds, to significant large breasts. It is caused by an altered balance between estrogens and androgens (increased estrogens, decreased androgens, or increased sensitivity of breast tissue to estrogens). Increased leptin levels as well as human chorionic gonadotropin (hCG) and luteinizing hormone (LH) receptors on male breast tissue may also play a role. It must be distinguished from lipomastia or pseudogynecomastia (increased adipose tissue in the breast area), a common finding in obese children. Glandular tissue feels firm or grainy, while adipose tissue feels soft. Distinction may be difficult because the two conditions often coexist. Symptomatic benign gynecomastia, which may be a sign of hypogonadism or systemic disease, is far less common, while breast cancer is extremely rare.

PATHOPHYSIOLOGY

Neonatal gynecomastia occurs due to maternal estrogen, and subsides spontaneously in a few weeks. In early puberty, estrogen levels rise before androgens increase, creating conditions for development of breast buds. In addition, aromatase activity in muscle, skin and adipose tissue converts adrenal/testicular androgens (testosterone and androstenedione) to estrogens (estradiol and estrone). Extraglandular aromatization is enhanced in obese children. Estrogens cause proliferation of ductules and stroma and increase in vascularity. As puberty progresses, androgen levels rise, and glandular tissue regresses. If normal regression does not occur, stromal fibrosis predominates, with few ductules remaining. On testing, serum levels of testosterone (T), estradiol (E2), and dehydroepiandrosterone sulfate (DHEAS) are normal. Free T may be raised; but outside the research setting, this test is so unreliable that there is little benefit in measuring it in routine clinical practice.

The common pathological causes of gynecomastia are listed in **Table 1**. Gynecomastia may be induced by high estrogen levels in estrogen-secreting tumors (e.g., Leydig cell, Sertoli cell, hCG-producing, or adrenocortical tumors). Androgen levels may be low due to primary gonadal failure (e.g., Klinefelter syndrome, orchitis, or castration) or secondary (hypothalamic-pituitary) gonadal failure (e.g., craniopharyngioma, brain tumors, or cranial radiation). Alternatively, there may be impairment of androgen action (androgen insensitivity syndrome) or androgen receptors (gene defects, or drugs). Altered levels of sex hormone-binding globulin (e.g., hyperthyroidism, chronic liver disease, or drugs) can change the estrogen-androgen ratio.

CLINICAL PRESENTATION

Presence of breast tissue in the neonate or adolescent boy can cause much parental anxiety. In the neonate massaging or pressing breast buds to *remove the toxins* may increase their size, and even

Table 1 Pathological causes of gynecomastia

- *Estrogen-secreting tumors*
  - Leydig cell tumor
  - Sertoli cell tumor
  - hCG-producing tumor
  - Adrenocortical tumor

- *Androgen deficiency*
  - *Primary hypogonadism*
    - Klinefelter/Kallmann syndrome
    - Congenital anorchia
    - *Testicular injury*: Infection (e.g., mumps), trauma, radiation, drugs (cytotoxic drugs, e.g., vincristine, methotrexate, cisplatin, imatinib)
  - *Secondary hypogonadism*
    - Hypothalamic-pituitary disease/surgery/radiation, e.g., craniopharyngioma
    - GnRH agonists/antagonists
    - *Abnormal testosterone synthesis*: Genetic defects, drugs (ketoconazole, spironolactone, flutamide, finasteride and dutasteride, etomide, metronidazole, cimetidine)
    - *Abnormal testosterone action*: Androgen insensitivity syndromes or androgen receptor gene defect
    - Abnormal sex-hormone binding globulin: Hyperthyroidism, chronic liver disease, drugs

elicit a few drops of milk. All that is needed is advice to leave well alone.

Adolescent gynecomastia typically occurs at age 11–15 years (early to midpuberty) and subsides in 1–2 years **(Figs 1A and B)**. The embarrassed adolescent may stop socializing or participating in sports activities, especially swimming, which can worsen obesity and therefore lipomastia. Careful history, examination and anthropometry are needed **(Table 2)**. Family history may be present. History of drug intake may have to be elicited with sensitivity because it may not be immediately forthcoming. For example, food supplements and herbal preparations may not be mentioned as parents may think of them as *only vitamins* or *natural, so safe*; estrogen containing creams may be thought of as cosmetics rather than medication; and history of using illicit drugs may not be given for obvious reasons.

On examination, breast tissue should be distinguished from fat and other masses (lipoma, dermoid, sebaceous cyst, ductal ectasia, or hematoma). **Table 3** lists some of the major causes of concern during the evaluation of gynecomastia.

APPROACH TO MANAGEMENT

If lipomastia, rather than glandular tissue is present, then investigations directed at obesity, advice on weight loss, and occasionally liposuction, are needed. Local causes (e.g., lipoma) need removal. Underlying pathology (e.g., hyperprolactinemia) need appropriate treatment. If gynecomastia is due to drugs, exposure should be stopped or minimized. In the rare instance of malignancy, mammogram and workup accordingly is needed. For physiological gynecomastia, psychological distress should be addressed, and follow-up advised. If spontaneous regression does not occur, medical therapy may be tried. From the sketchy evidence available, it works best in the initial 1–2 years before glandular tissue is replaced by fibrous tissue; side effects are minimal.
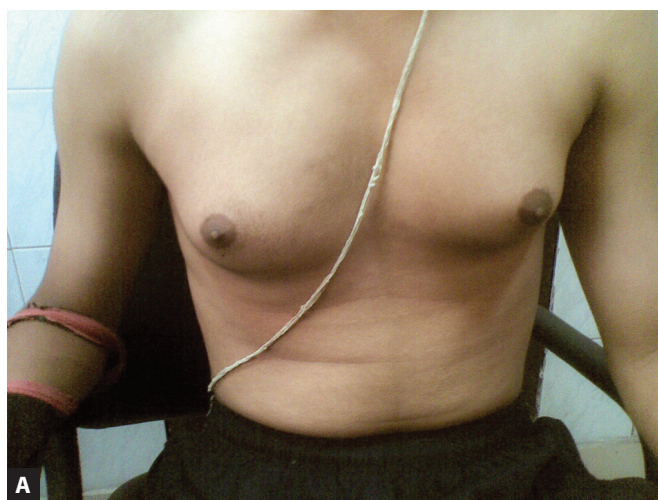
Figures 1A and B Gynecomastia in an adolescent boy. (A) Front view; (B) Lateral view

Table 2 History and examination in evaluation of gynecomastia

History

- Age at onset, duration, pain, discharge
- Puberty:
  - Presence and duration of pubic, axillary, facial hair
  - Gonadal changes, erections
- History of drug use:
  - Prescription drugs
  - Supplements, food supplements
  - Herbal preparations
  - Estrogen or phytoestrogen containing creams
  - Recreational and illicit drugs: anabolic steroids for body building, alcohol, marijuana, heroin, amphetamines
- Undescended testes, mumps
- *Systemic disease*: Recent weight gain/loss; known liver, kidney, CNS disease
- Degree of distress caused

Examination

- General:
  - Height, weight, BMI, body proportions (normal/eunuchoid)
  - Virilization (voice, muscle mass, facial and body hair)
- Pubertal:
  - Testicular size/mass
  - Stretched penile length
  - Pubic hair staging
- Local:
  - Size of breast
  - Glandular/adipose tissue
  - Symmetrical/asymmetrical: bilateral/unilateral
  - Tender/painless
  - Overlying skin
  - Discharge
  - Local lymph nodes
- *Systemic*: Thyroid, stigmata of liver/kidney/CNS disease
- Abdominal mass

Table 3 Cause for concern in evaluation of gynecomastia

- *Age*: Onset at age < 9 years
- Local:
  - Breast tissue is hard or fixed.
  - Breast tissue not under the nipple
  - Discharge: serosanguineous/galactorrhea
  - Tethering or other skin changes
  - Presence of lymphadenopathy
  - Breast tissue > 5 cm (macromastia)
- Systemic:
  - Evidence of systemic illness
  - Hypogonadism: testes < 4 mL

Table 4 Therapeutic options for gynecomastia

- Medical therapy:
  - Block effect of estrogens: selective estrogen receptor modifiers (SERMs)
    - Tamoxifen, raloxifene, clomiphene
  - Decrease estrogen production: aromatase inhibitors
    - Anastrazole, letrozole, testolactone
  - Counteract estrogen effect: androgens
    - Danazol
- Surgery:
  - Reduction mammoplasty: open/minimally invasive
  - Liposuction
  - Combination
- *Compression garments* (camouflage, stabilize bouncing tissue)

In longstanding cases, with macromastia, if medical therapy fails or if medical therapy is not tolerated), the definitive option of surgery **(Table 4)**, or compression garments (for camouflage, and to stabilize bouncing tissue) can be offered. Subcutaneous mastectomy using a peri- or circumareolar incision or recent minimally invasive techniques is needed. If significant sagging skin is present, an inframammary approach may be needed. Liposuction

may be needed for excess adipose tissue. Complications include bleeding, excessive removal of tissue and scarring, and nerve/skin/muscle damage.

Investigations are needed for onset before age 9 years, if there is associated illness, galactorrhea/other discharge, the cause is not clear, or the breast size is large or increasing. Thyroid, liver and kidney function tests, LH, FSH and gonadal steroids, prolactin, hCG, and a test for Cushing syndrome, may be needed. Imaging can be planned accordingly (e.g., scrotum or abdomen if serum estradiol (E2) or hCG is raised suggesting

a hormone-secreting tumor). Treatment depends on the cause identified: resection of an E2 or hCG-secreting tumor, hormone replacement for hypogonadism, etc. With androgen replacement for hypogonadism, paradoxically, the breast tissue may increase, due to aromatization of the added androgen into estrogen, and surgery may be required, as above.

MORE ON THIS TOPIC

Johnson RE, Hassan Murad M. Gynecomastia: pathophysiology, evaluation, and management. Mayo Clin Proc. 2009;84:1010-5.

Lawrence SE, Faught KA, Vethamuthu J, Lawson ML. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. J Pediatr. 2004;145:71-6.

Nordt CA, DiVasta AD. Gynecomastia in adolescents. Curr Opin Pediatr. 2008;20:375-82.

IN A NUTSHELL

1. Gynecomastia is a common physiological, self-limiting condition in neonates, adolescents and the elderly.
2. It is caused by altered estrogen/androgen ratio or sensitivity.
3. It must be distinguished from lipomastia, with which it may coexist.
4. Investigations are needed if there is prepubertal onset, associated disease or hypogonadism, discharge, hard fixed tissue, or increasing size. The underlying cause must be treated.
5. Emotional distress should be addressed; weight loss may be needed.
6. Medical therapy may be offered if regression does not occur; surgery is definitive.

Chapter 44.14

Normal Development and Physiology of the Adrenal Gland

Rajesh Joshi

The adrenal glands are paired bodies lying cranial to the kidneys (hence also called suprarenal glands) within the retroperitoneal space. The glands consist of two layers: the cortex and the medulla.

DEVELOPMENT

The cortex and medulla of the adrenal gland have different origins. The cortex develops during the sixth week as an aggregation of mesenchymal cells on each side, between the root of the dorsal mesentery and the developing gonad. The cells of the fetal cortex develop from the mesothelium that lines the posterior abdominal wall. The medulla is formed from cells of adjacent sympathetic ganglion, which is derived from the neural crest. The neural crest cells form a mass on the medial side of the fetal cortex. As they are surrounded by the fetal cortex, these cells differentiate into the secretory cells of the suprarenal medulla.

Later more mesenchymal cells arise from the mesothelium and enclose the fetal cortex. These cells give rise to the permanent cortex. The zona glomerulosa and fasciculata are present at birth, but the zona reticularis is not recognizable until about the end of the third year. The adrenal glands rapidly become smaller as the fetal cortex regresses during the first year and do not regain their original weight until the end of the second year.

PHYSIOLOGY OF ADRENAL CORTEX

The adrenal cortex secretes three types of hormones:
1. *Mineralocorticoids* (principally aldosterone), by the zona glomerulosa which forms 5–10% of cortex.
2. *Glucocorticoids* (principally cortisol), by the zona fasciculata which occupies the major volume of cortex.
3. *Androgens* [mainly dehydroepiandrosterone (DHEA)], by the zona reticularis.

There is a continuous migration of the cells of zona glomerulosa to zona reticularis through the fasciculata. As these cells migrate their hormonal products change. Why this occurs is not clear. The final differentiation of the three zones occurs by around 8 years.

Adrenocortical production of hormones begins in embryonic life at about 7 weeks of gestation. All adrenocortical hormones are steroid compounds derived from cholesterol. Cholesterol is obtained mostly from circulating low-density lipoproteins (LDL) which is further hydroxylated to form various intermediate steroidogenic products before the three major types of adrenal hormones are synthesized. **Figure 1** depicts the synthesis of adrenocortical hormones.

Steroidogenic acute regulatory protein (StAR) mediates the rapid action of adrenocorticotropic hormone (ACTH) on the adrenal by facilitating rapid movement of cholesterol from the outer to the inner mitochondrial membrane, where it is converted to pregnenolone by the P450scc enzyme by the removal of a side chain. This is the rate determining step of adrenocortical hormone production. Hydroxylation reactions occur in the mitochondria and endoplasmic reticulum converting pregnenolone into specific hormones.

The enzymes **(Table 1)** CYP11A, CYP11B1, CYP11B2, CYP17 and CYP21 are cytochrome P450 hemoproteins. The first three enzymes are located in mitochondria, whereas the remaining enzymes are present in the endoplasmic reticulum.
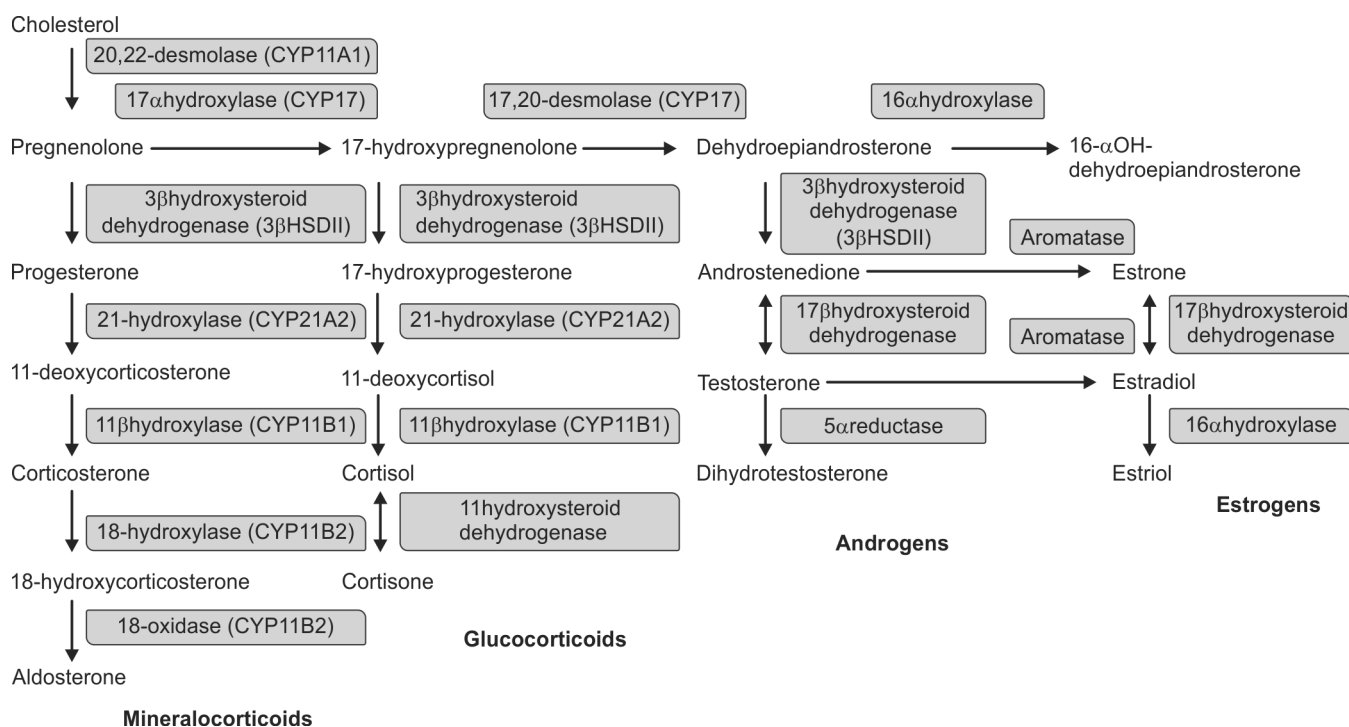
Figure 1 Adrenocortical steroid biosynthesis

Table 1 Various steroid biosynthetic enzymes and their genes

Enzyme	Chromosome	Gene
Cholesterol side chain cleavage		
(20-hydroxylase, 22-hydroxylase, 20,22-lyase)	15q23-24	CYP11A
3ß-Hydroxysteroid dehydrogenase (3ß-HSD)	1p13.1	3ß-HSD
17α-Hydroxylase and 17,20-lyase	10q24-25	CYP17
21-Hydroxylase	6p21	CYP21
11ß-Hydroxylase	8q22	CYP11B1
Aldosterone synthetase		
(11ß-hydroxylation, 18-hydroxylation, and 18-oxidation)	8q22	CYP11B

The Hypothalamic-Pituitary-Adrenal Axis

Cortisol is secreted in response to ACTH secreted from the pituitary, which in turn is stimulated by corticotropin-releasing hormone (CRH), and to some extent by arginine vasopressin (AVP) from the hypothalamus. ACTH which has a half-life of few minutes in blood is a peptide containing 39 amino acids derived from pro-opiomelanocortin (POMC). The first 20–24 amino acids of ACTH are needed for its full biological activity. ACTH interacts with receptors which stimulate cAMP production, thus eliciting its acute and long-term effects.

The characteristics of cortisol secretion are circadian rhythm which responds mainly to light and darkness; its pulsatility—the frequency and amplitude of which is greater in the morning; stress-induced secretion and negative inhibition by glucocorticoids. The hormones of the axis show a diurnal rhythm with CRH peaking early in the morning at about 4 am, followed by ACTH which peaks around 6 am and then cortisol at around 8 am. The diurnal rhythm which starts establishing by 0.5–1 year of age, takes around 3 years of age to become fully established.

There is an equilibrium between the secretion of cortisol and ACTH which is disturbed when plasma levels of cortisol increases leading to negative feedback of CRH and ACTH. *POMC* gene transcription is inhibited by prolonged exposure of glucocorticoids.

Cortisol

Most of the cortisol is bound to corticosteroid-binding globulin (transcortin). The unbound fraction (2–3%) binds to specific glucocorticoid receptor on target cells, which activates transcription of genes and further biological activity of the hormone. Most cortisol is metabolized by the 11β-hydroxysteroid dehydrogenase system to cortisone which is a reversible process.

Cortisol has a permissive action, i.e., without cortisol, certain chemical reactions within cells will not occur, e.g., the production of epinephrine and glucagon. Cortisol is a stress hormone—in times of stress, it is released and enhances the effect of norepinephrine on blood pressure. Cortisol has effects generally opposite of insulin—increases blood glucose concentrations by its action on glycogen, protein, and lipid metabolism but stimulates liver glycogen storage. It stimulates gluconeogenesis in liver and decreases utilization of glucose in other tissues. It activates lipolysis in adipose tissue which releases free fatty acids in circulation. It causes insulin resistance and reduces protein synthesis in muscles. Cortisol stimulates appetite and causes central obesity as in Cushing syndrome. It has anti-inflammatory action and suppresses tissue response to injury. It impairs cellular and humoral immunity.

Cortisol though a glucocorticoid hormone, can have mineralo-corticoid effect in large amounts. In normal children of various ages and in adult subjects, the rate of cortisol secretion increases with body size. When the values are corrected for body surface area, the rates are similar at various ages, the average being 6 mg/m^2/24 hour.

Aldosterone and Renin-Angiotensin-Aldosterone System

Aldosterone acts mainly in the distal tubule and the collecting ducts of the nephron to cause conservation of sodium, secretion of potassium, increased water retention and increased blood pressure. Aldosterone is physiologically mainly bound to albumin. Rate of aldosterone synthesis is 100–1,000 fold lower than cortisol, the levels being 15–30 ng/dL (low sodium diet) and 2–12 ng/dL (normal sodium diet). Aldosterone is regulated mainly by renin-angiotensin system and to some extent by ACTH. Renin is a proteolytic enzyme that converts angiotensinogen in liver to angiotensin I, which has mild vasopressor effect. Cleavage of angiotensin I by acetylcholinesterase (ACE) in lungs produces angiotensin II which is a potent vasoconstrictor which stimulates aldosterone production.

The renin-angiotensin-aldosterone system is active by around 16 weeks of gestational age. In the neonatal period, a relative state of aldosterone resistance exists with average level in term newborn being about 80 ng/dL (2,200 pmol/L). During the first year of age, there is a steep and progressive decline in aldosterone to prepubertal concentrations. Aldosterone has half-life of 10–20 minutes as opposed to 1–2 hours for cortisol.

Androgens

Dehydroepiandrosterone, its sulfate (DHEAS) and androstene-dione are the adrenal androgens which are secreted in large amounts during fetal life. The adrenals secrete these androgens in small quantities after the first year of life till the onset of adrenarche. Adrenarche is an event independent of gonadarche occurring around 6 years of age and is associated with androgen-dependent body hair growth (pubarche) including hair over the groin and axilla. ACTH is a possible initiator of adrenarche. Adrenal androgen production is also discussed in Chapter 44.15 in the context of congenital adrenal hyperplasia.

Steroid Catabolism

About 1% of plasma aldosterone and cortisol is excreted in urine unchanged. The main site of steroid inactivation and catabolism is the liver. The steroids are conjugated to form hydrophilic molecules (glucuronides and sulfates) and these inactive hormones are mainly eliminated in urine. The measurement of these urinary metabolites can be used to diagnose adrenal disorders.

ADRENAL MEDULLA

The adrenal medulla is different in development, structure and function from the cortex. It releases epinephrine and to some extent norepinephrine, as well as peptides from the chromaffin granules into the bloodstream due to direct stimulation by acetylcholine release from sympathetic nerves. This helps to regulate the blood pressure, blood flow and the vascular resistance. The released catecholamines have a short half-life of 1–2 minutes. They are taken up by the neurons and either retransported as storage vesicles or deaminated and methylated or oxidized. The liver degrades the catecholamines to vanillyl mandelic acid (VMA).

IN A NUTSHELL

1. The adrenal cortex secretes three classes of hormones: the glucocorticoids, the mineralocorticoids and the androgens.
2. All adrenocortical hormones are derived by hydroxylation of cholesterol by a series of enzymes belonging to the cytochrome P450 system.
3. Cortisol production has a diurnal rhythm with pulsatility and is regulated by the hypothalamic-pituitary-adrenal axis through ACTH and CRH.
4. Aldosterone secretion is regulated by renin-angiotensin system and to some extent by ACTH.
5. Adrenal medulla releases epinephrine and norepinephrine.

MORE ON THIS TOPIC

Greaves RF, Jevalikar G, Hewitt JK, Zacharin MR. A guide to understanding the steroid pathway: new insights and diagnostic implications. Clin Biochem. 2014;47:5-15.

Migeon CJ, Lanes R. Adrenal disorders and sexual development abnormalities. In: Lifshitz F. Pediatric Endocrinology. 5th ed. New York: Informa Healthcare; 2007. pp. 195-271.

Miller WL. The adrenal cortex and its disorders. In: Brook C, Clayton P, Brown R. Brooks Clinical Pediatric Endocrinology. 5th ed. Blackwell Publishing; 2005. pp. 293-351.

Miller WL, Achermann JC, Fluck CE. The adrenal cortex and its disorders. In: Sperling MA. Pediatric Endocrinology. 3rd ed. Philadelphia: Saunders; 2008. pp. 444-511.

Chapter 44.15
Congenital Adrenal Hyperplasia
Anurag Bajpai, PSN Menon

Congenital adrenal hyperplasia (CAH) comprises of a group of autosomal recessive steroidogenic defects characterized by decreased cortisol production with mineralocorticoid and/or androgen excess or deficiency. The disorder presents with myriad clinical manifestations ranging from lethal salt wasting (SW) crisis, failure to thrive, disorder of sexual differentiation, early or delayed puberty to low renin hypertension. Timely identification is mandatory to ensure successful outcome.

PATHOPHYSIOLOGY

Understanding of steroidogenic pathway is central to delineating pathophysiology of CAH **(Fig. 1)**. Steroidogenesis is a complex process involving conversion of cholesterol to steroid hormones under the control of a group of P450 enzymes. The transfer of cholesterol into mitochondria is the first endocrine regulated step in steroidogenesis mediated by the adrenocorticotropic hormone (ACTH) dependent steroidogenic acute regulatory protein (StAR). The key step in steroidogenesis is conversion of progesterone and 17-hydroxyprogesterone (17 OHP) to deoxycorticosterone (DOC) and 11-deoxycorticosterone (11 DOC) by the enzyme 21-hydroxylase (P450c21). These metabolites have weak mineralo-corticoid activity which accounts for the hypertension seen in children with 11β-hydroxylase (P450c11AS and P450c11β) and 17α-hydroxylase (P450c17) deficiencies. The production of cortisol and aldosterone requires 11-hydroxylation, a process mediated by the enzyme 11β-hydroxylase, P450c11AS in zona glomerulosa and P450c11β in zona fasciculata.

CLASSIFICATION

Common to all forms of CAH is cortisol deficiency, which triggers ACTH production resulting in accumulation of metabolites prior to the block. The manifestations of the disease thus represent deficiency (distal to block) or excess (proximal to block) of the steroid/s **(Table 1)**.

21-HYDROXYLASE DEFICIENCY

21-hydroxylase deficiency (21 OHD) is the most common form of CAH accounting for 95% of all cases. It may be lethal if untreated emphasizing the need for early diagnosis and treatment.

Clinical Spectrum
The manifestations of 21 OHD are dependent on the residual 21-hydroxylase activity and vary from SW crisis at birth to prenatal virilization to mild hyperandrogenism later in life **(Table 2)**.

Salt Wasting Form
These children have the most severe form of 21-hydroxylase deficiency and present in the neonatal period with SW crisis around 2–6 weeks of life. Pointers to diagnosis include failure to thrive, vomiting, pigmentation, lethargy, abnormal genital appearance and shock with normal urine output. Salt wasting form of 21 OHD should be suspected in all sick neonates after exclusion of infection. Biochemical findings indicative of SW crisis include hyponatremia, hyperkalemia, hemoconcentration, hypoglycemia and metabolic acidosis.

Simple Virilizing Form
These individuals have a milder defect with mineralocorticoid secretion sufficient to prevent salt wasting. Girls present with genital ambiguity while boys have peripheral precocious puberty. The diagnosis is often delayed due to lack of salt wasting. Boys are usually diagnosed at a very late age with significant bone age advancement and compromised final height. Some girls may be virilized to the extent of being reared as boys and present with cyclical hematuria during adolescence.

Nonclassic
These children have very mild 21-hydroxylase deficiency with peripubertal hyperandrogenism as the predominant manifestation. Clinical features in girls include precocious pubarche, secondary amenorrhea, menstrual irregularity, hyperandrogenism (hirsutism, androgenic alopecia, or refractory cystic acne) and infertility.

Epidemiology
The prevalence of 21 OHD is one in every 10,000–20,000 live births. Case finding based studies suggested equal prevalence of
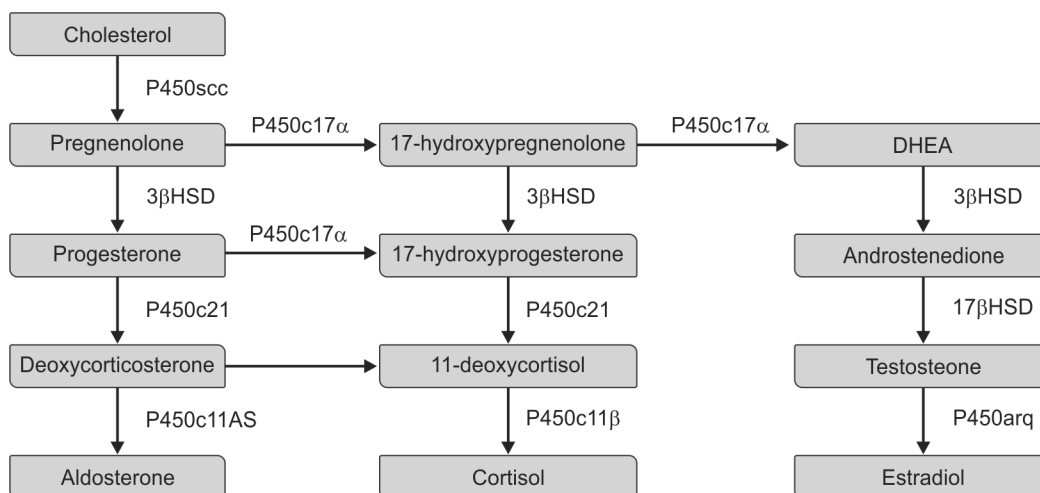
Figure 1 Steroidogenic pathway
Abbreviations: SCC, side chain cleavage enzyme; HSD, hydroxysteroid dehydrogenase; DHEA, dehydroepiandrosterone.

Table 1 Comparison of common forms of congenital adrenal hyperplasia

Enzymes involved	Androgen	Blood pressure	Presentation		Diagnosis	Treatment
			Boys	Girls		
21 hydroxylase						
Salt wasting	High	Low	Precocious puberty	Ambiguity	17 OHP*	HC, Fludrocortisone
Simple virilizing	High	Normal	Precocious puberty	Ambiguity	17 OHP*	HC, Fludrocortisone
Nonclassic	High	Normal	Normal	Hirsutism	17 OHP*	HC
11β-hydroxylase	High	High$	Precocious puberty	Ambiguity	DOC, 11-DOC	HC, Spironolactone
3β-HSD	Variable#	Low	Ambiguity	Ambiguity	ACTH stimulation test**	HC, Fludrocortisone
17-hydroxylase/ lyase	Low	High$	Ambiguity	Delayed puberty	DOC, 18-OHDOC	HC
StAR	Low	Low	Ambiguity	Delayed puberty	Low 17 OHP	HC, Fludrocortisone

Abbreviations: HSD, hydroxysteroid dehydrogenase; StAR, steroidogenic acute regulatory protein; 17 OHP, 17-hydroxyprogesterone; DOC, deoxycorticosterone; HC, hydrocortisone; 11-DOC, 11-deoxycorticosterone; 18-OHDOC, 18-hydroxycorticosterone.
* Basal and ACTH stimulated
** Ratio of pregnenolone, progesterone, 17-hydroxypregnenolone to 17OHP and DHEA to androstenedione after ACTH stimulation
$ Due to mineralocorticoid effect of DOC, however, BP may also be normal
# Due to peripheral conversion of DHEA

Table 2 Comparison of forms of 21-hydroxylase deficiency

Feature	Salt wasting	Simple virilizing	Nonclassic
Age at presentation			
Girls	Neonatal period	Neonatal period	Late childhood
Boys	Neonatal period	Childhood	Missed
Salt wasting crisis	Yes	No	No
Virilization			
Prenatal	Yes	Yes	No
Postnatal	Yes	Yes	Yes
Ambiguous genitalia	Yes	Yes	No
Plasma renin activity	High	High, normal	Normal
Treatment			
Hydrocortisone	Yes	Yes	Yes
Fludrocortisone	Yes	Yes	No
Salt	Yes	No	No

SW and simple virilizing (SV) forms and a predilection for girls. The figures are even more striking in developing countries where girls with salt wasting far outnumber boys indicating death of boys due to delayed diagnosis. Neonatal screening has demonstrated that the condition affects boys and girls equally, as expected from an autosomal recessive disease.

Diagnosis
The diagnosis of 21 OHD is established by elevated 17 OHP levels in the presence of characteristic clinical picture. While low cortisol, aldosterone and elevated testosterone and ACTH levels are hallmarks of 21 OHD, they have limited role in establishing the diagnosis of 21 OHD.

Timing
17-hydroxyprogesterone levels should be performed in the morning. In the neonatal period, the levels should be measured after 48 hours of life due to the confounding effect of neonatal surge. ACTH stimulation test (measurement of 17 OHP levels one hour after 250 μg of intravenous ACTH) should be done in individuals with borderline 17 OHP levels.

Interpretation
Basal 17 OHP levels are markedly elevated in classic forms (both SW and SV) at more than 10,000 ng/dL (300 nmol/L). Levels greater than 200 ng/dL (6 nmol/L) must be investigated further by ACTH stimulation, while those less than 200 ng/dL (6 nmol/L) are normal **(Table 3)**. Following ACTH stimulation, the levels increase beyond 10,000 ng/dL (300 nmol/L) in classic forms and 1000 ng/dL (30 nmol/L) in nonclassic form.

Diagnostic Issues
17-hydroxyprogesterone levels are falsely elevated in stressed and premature neonates. Lower levels are observed in neonates exposed to antenatal steroids. Mild elevation of 17 OHP disproportionately low for the clinical picture is observed in 11β-hydroxylase deficiency and 3β-hydroxysteroid deficiency (3βHSD). They can be differentiated from 21 OHD by the lack of salt wasting (11 OHD) and high 17-hydroxypregnenolone to 17 OHP ratio (3βHSD).

Management
Management of 21 OHD is a medical emergency requiring early identification and timely intervention. Regular follow-up and monitoring are associated with normal growth, intellectual and reproductive outcome.

Acute Urgent initiation of hydrocortisone is mandatory in children with suspected SW form of 21 OHD. This should be done after obtaining sample for 17 OHP. Hydrocortisone should be given as a bolus of 50 mg/m^2 followed by 100 mg/m^2/day in four divided doses. Supportive treatment includes aggressive fluid resuscitation (normal saline 20 mL/kg followed by double maintenance fluids), dextrose bolus, antihyperkalemic measures and hypertonic saline. Hydration status, blood glucose and electrolytes should

Table 3 Classification of 21-hydroxylase deficiency according to 17OHP levels

Basal	ACTH stimulated	Disease form
> 10,000 ng/dL	> 10,000 ng/dL	Classic (both salt wasting and simple virilizing)
200–10,000 ng/dL	1000–10,000 ng/dL	Nonclassic
200 ng/dL	< 1,000 ng/dL	Normal

be monitored. Treatment with hydrocortisone is associated with dramatic improvement. The dose of hydrocortisone is decreased to 20 mg/m^2/day over the next three days. Mineralocorticoid supplementation should be started after hydrocortisone dose is reduced below 50 mg/m^2/day. A key aspect of management is educating the family about the disease, the need for long-term treatment, stress dosing and regular monitoring. Written instruction for stress dosing and emergency care should be provided.

Long-term The aim is to correct glucocorticoid and mineralocorticoid deficiency and suppress androgen production.

Glucocorticoids

Glucocorticoids should be given in all children with classic 21OHD and in those with nonclassic form of disease with refractory acne, infertility and hirsutism.

Formulation The choice of glucocorticoid preparation is determined by its potency and growth inhibitory effect. The growth inhibitory effects of synthetic corticosteroids such as prednisolone and dexamethasone are disproportionately greater than their anti-inflammatory potency. Hydrocortisone is thus the preferred agent in the growing children. It has the added advantage of intrinsic mineralocorticoid activity. Prednisolone and dexamethasone may be used after linear growth is completed in individuals with persistently elevated 17 OHP levels despite high hydrocortisone dose.

Dose The endogenous glucocorticoid production rate is 6–8 mg/m^2/day. Maintaining an optimal dose is desirable as while low glucocorticoid dose leads to rapid skeletal maturation and compromised final height, supraphysiological dose is associated with growth failure. The recommended dose is 10–15 mg/m^2/day for hydrocortisone, 2.5 mg/m^2/day for prednisolone and 0.5 mg/m^2/day for dexamethasone. Dose greater than 20 mg/m^2/day of hydrocortisone equivalent is associated with growth retardation.

Frequency Hydrocortisone should be given thrice daily. There is no benefit of higher dose in the morning. Prednisolone should be given in twice and dexamethasone in once daily dose.

Stress dosing Children with 21 OHD are unable to mount a stress response predisposing them to fatal consequences during stress. This mandates the need to increase hydrocortisone dose during stress. The dose should be doubled during fever, diarrhea and respiratory infections. It should be trebled during severe infections like pneumonia. Children with recurrent vomiting, dehydration or shock should be given intravenous steroid bolus (50 mg/m^2 stat) followed by 100 mg/m^2/day in four divided doses. The doses should be tapered after reversal of stress.

Mineralocorticoids

Mineralocorticoid replacement is required in both SV and SW types of 21 OHD. The only preparation available is fludrocortisone as 100 µg tablet. The requirement for fludrocortisone is substantially higher in the neonatal period due to relative mineralocorticoid resistance to the range of 200–300 µg. Subsequently, the dose is around 100 µg daily. There is no need for increasing the dose of mineralocorticoids during stress.

Salt

All infants with SW form should be given 1–2 grams of salt daily as mineralocorticoid therapy is ineffective without adequate body salt. Salt supplementation is not required after infancy.

Monitoring

Children with 21 OHD should be monitored for adequacy of treatment, growth and adverse effects of overtreatment. Monthly follow-up is required during the first 6 months of life and 2 monthly thereafter. Evaluation should include assessment of blood pressure, pubertal status, growth, serum electrolytes and 17 OHP. 17 OHP levels should be maintained in the high normal levels (800–1,000 ng/dL, 24–30 nmol/L) as overzealous control results in glucocorticoid excess. Plasma renin activity helps in deciding the adequacy of mineralocorticoid replacement in children with SW form. Bone age should be assessed annually.

Special Issues

Genital Surgery

Genital surgery is required in infancy in girls with severe virilization (Prader stage 3 and above). Special efforts should be made to avoid neural injury during surgery and clitoral recession. Vaginoplasty may be required during puberty.

Growth Promoting Strategies

Final height in children with 21 OHD is one standard deviation (7–10 cm) below target height. Delayed diagnosis, higher glucocorticoid dose during infancy and use of synthetic steroids are associated with compromised height. The use of aromatase inhibitors (to delay epiphyseal maturation) and antiandrogens (to counter the effect of elevated androgens) along with hydrocortisone and fludrocortisone for increasing final height is experimental. GnRH analogs are helpful in boys with rapid advancement in bone age and triggered central precocious puberty. Combination of growth hormone and GnRH analog may be used in children with marked advancement of bone age and compromised final height.

Reproductive Health

Inadequate treatment in girls results in hyperandrogenism with hirsutism, menstrual irregularities and acne. Increase in dose of glucocorticoid or the use of a more potent agent like dexamethasone may reverse these changes. Adequate treatment is essential before planning pregnancy. Special care should be taken to avoid dehydration and dyselectrolytemia. Dexamethasone crosses the placenta and should be avoided. Management during labor includes hydrocortisone infusion, adequate fluid replacement and frequent electrolyte monitoring.

Skeletal Health

The use of long-term steroids has resulted in the speculation of compromised bone health in 21 OHD. Use of physiological dose of hydrocortisone and calcium and vitamin D supplementation reduces the risk of reduced bone mass. Routine estimation of bone mineral density is not required.

Prenatal Diagnosis and Treatment

Parents of a child with 21 OHD often desire prenatal diagnosis. This helps in deciding the need for antenatal treatment to prevent virilization in girls. Most parents in developing countries do not want to continue pregnancy with an affected child. Prenatal diagnosis is done through chorionic villus sampling at 8–10 weeks of gestation to identify the mutation present in the family or by estimating 17 OHP levels in amniotic fluid around 16–18 weeks of gestation. Prenatal treatment of mother with dexamethasone to prevent fetal virilization is controversial and recommended in research settings only. The treatment has to be started at 6 weeks

of gestation and continued throughout the pregnancy in affected girls (one in eight pregnancies). This implies the use of steroids for a long period without any benefit in seven out of eight pregnancies. Steroid treatment significantly reduces the extent of virilization at birth; the adverse effects on mother and potential long-term impact on children however questions the strategy.

Neonatal Screening

21 OHD has many attributes that make it an attractive disease for neonatal screening. It is reasonably common (1 in 10,000–15,000 live births), often missed at birth (particularly in boys), has life-threatening consequences and amenable to effective treatment. Neonatal screening for 21 OHD has been widely practiced in USA and several developed countries. Screening has traditionally been done on day 3 of life with 17 OHP levels. The confounding factors include high false positive rate, effect of stress and prematurity and antenatal steroids. This has resulted in the recommendation of two-tier screening tests with immunoassay based 17 OHP at the first stage and liquid chromatography/tandem mass spectrophotometry in those with positive tests.

RARE FORMS OF CONGENITAL ADRENAL HYPERPLASIA

11β-Hydroxylase Deficiency

11β-hydroxylase (P450c11AS and P450c11β) deficiency is the second most common form of CAH. It is characterized by reduced cortisol and aldosterone (causing pigmentation) and elevated deoxycortisol (hypertension) and androgen levels (virilization). The condition is associated with virilization in girls and peripheral precocious puberty in boys. Boys often present with failure to thrive and polyuria with hypertension detected incidentally. The condition should be suspected in the presence of hyperpigmentation, hypokalemic alkalosis and hypertension. The diagnosis is established by elevated basal and ACTH stimulated 11 DOC levels. Treatment includes glucocorticoid replacement; mineralocorticoid supplementation is not required. Persistent hypertension should be treated with antialdosterone spironolactone.

3β-Hydroxysteroid Dehydrogenase Deficiency

3β-HSD is associated with low cortisol, aldosterone (salt wasting) and delta-5 steroids (undervirilization in boys) and elevated delta-4 steroids (virilization of girls). Salt wasting crisis is common in infancy. These children have mildly elevated 17 OHP though the levels are markedly lower than those in 21 OHD. Diagnosis is confirmed based on ACTH stimulated 17-hydroxypregnenolone to 17 OHP ratio. Treatment is similar to 21 OHD; age appropriate androgen replacement is required for boys affected with the condition.

17β-Hydroxylase Deficiency

The key biochemical abnormalities in 17β-hydroxylase (P450c17) deficiency include low cortisol (pigmentation) and androgen levels (undervirilization in boys) and elevated mineralocorticoid precursors (hypertension). Presentation is usually with pigmentation, genital ambiguity in boys, delayed puberty in girls and hypokalemic alkalosis. High levels of 11 DOC and pregnenolone are diagnostic. Treatment includes physiological hydrocortisone and spironolactone for hypertension.

Steroidogenic Acute Regulatory (StAR) Protein Deficiency

Steroidogenic acute regulatory protein deficiency is associated by reduced transfer of cholesterol from cytoplasm to mitochondria resulting in reduced steroidogenesis and accumulation of cholesterol in cytoplasm. The disorder is associated with reduced production of all three classes of steroids resulting in SW crisis, pigmentation, genital ambiguity in boys and delayed puberty in girls. The diagnosis is established by demonstration of low basal and ACTH stimulated 17 OHP and 17-hydroxypregnenolone levels. Congenital adrenal hypoplasia is a close differential and can be differentiated by the demonstration of adrenal size on ultrasound. Treatment includes hydrocortisone and fludrocortisone.

P450 Oxidoreductase Deficiency

P450 oxidoreductase (POR) is the protein that transfers electrons from NADPH to all forms of cytochrome P450 enzymes, including P450c17, P450c21 and P450aro. Clinical and hormonal manifestations of deficiency may vary suggesting partial deficiencies of both 17α-hydroxylase and 21-hydroxylase. These include ambiguous genitalia, cortisol deficiency and multiple skeletal abnormalities (Antley-Bixler syndrome).

IN A NUTSHELL

1. 21 hydroxylase deficiency (21 OHD) should be considered in all children with failure to thrive, hyponatremia and hyperkalemia, ambiguous genitalia and boys with peripheral precocious puberty.
2. Basal and ACTH stimulated 17 OHP levels are the diagnostic investigations in 21 OHD.
3. Hydrocortisone is preferred to prednisolone and dexamethasone in growing children.
4. Fludrocortisone should be given even in the absence of overt salt wasting.
5. 11β-hydroxylase deficiency should be considered in children with hypertension and hypokalemic alkalosis.
6. Glucocorticoid dose should be increased during periods of stress.
7. Salt supplementation is essential in all infants with SW form of 21 OHD.

MORE ON THIS TOPIC

Auchus RJ, Witchel SF, Leight KR, et al. Guidelines for the Development of Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol. 2010;2010:2752-13.

Bajpai A, Kabra M, Menon PS. 21-hydroxylase deficiency: clinical features, laboratory profile and pointers to diagnosis in Indian children. Indian Pediatr. 2004;41:1226-32.

Bajpai A, Pandey RM, Kabra M, Menon PS. Growth pattern and final height in 21-hydroxylase deficiency. Indian Pediatr. 2007;44:771-3.

Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet. 2005;365: 2125-36.

Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:4133-60.

Chapter 44.16
Adrenal Insufficiency and Polyglandular Failure

M Vijayakumar

Adrenal insufficiency is a life-threatening disorder of adrenal gland which results from either adrenal insufficiency or adrenal failure secondary to hypothalamic or pituitary causes. Deficiency of glucocorticoids often with associated deficiency of mineralocorticoids and adrenal androgens produce the characteristic clinical manifestations. It is less frequent in children compared to adults.

ETIOLOGY AND EPIDEMIOLOGY

Adrenal insufficiency is classified as primary or secondary. Primary adrenal insufficiency (Addison disease) is caused by diseases affecting the adrenal cortex. Addison disease refers to a group of disorders with common clinical presentation. Secondary or central adrenal insufficiency is caused by pituitary diseases that reduce the release of adrenocorticotropic hormone (ACTH) or from lesions in hypothalamus with impaired synthesis of corticotropin-releasing hormone (CRH). The most common cause of secondary adrenal insufficiency is iatrogenic hypothalamic-pituitary-adrenal (HPA) axis suppression due to glucocorticoid administration. The common causes of adrenal insufficiency are listed in **Box 1**.

Causes of adrenal disorders are also divided into acute and chronic, but most acute presentations have an underlying chronic process. Acute presentation may be precipitated by trauma, intercurrent illness, surgery or inadequate fluid and salt intake.

Currently, the most common precipitating cause is autoimmune destruction of the adrenal gland. Among infective causes, tuberculosis remains the most common cause even now followed by fungal infections. Addison disease can occur in isolation or as a part of autoimmune polyendocrinopathy syndromes. Genetic disorders such as adrenoleukodystrophy (X-linked recessive), congenital adrenal hypoplasia (X-linked recessive) and congenital adrenal hyperplasia (CAH) (autosomal recessive) also present with features of adrenal insufficiency.

Prevalence of chronic primary adrenal insufficiency in adult population is about 100 cases per million people, with autoimmune

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BOX 1   Causes of adrenal insufficiency

- *Primary adrenal insufficiency*
  - *Autoimmune disorders*: Autoimmune adrenalitis, APS
  - *Infections*: Tuberculosis, fungal infections (histoplasmosis, coccidioidomycosis), viral (HIV/AIDS)
  - *Drug induced*: Ketoconazole, imatinib
  - Congenital adrenal hyperplasia
  - Congenital adrenal hypoplasia
  - Adrenocortical unresponsiveness to ACTH (deficient ACTH receptor)
  - *Metabolic disorders*: Adrenoleukodystrophy, Zellweger syndrome, Wolman disease
  - *Adrenal hemorrhage*: In newborn, following infections
- *Central adrenal insufficiency*
  - Withdrawal from glucocorticoid therapy
  - Hypopituitarism
  - *Hypothalamic disorders*: Tumors, radiation, surgery

Abbreviations: APS, autoimmune polyglandular (polyendocrinopathy) syndrome; ACTH, adrenocorticotropic hormone; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

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adrenal insufficiency as the most common cause. In children, genetic forms like CAH (72%), adrenoleukodystrophy and adrenal hypoplasia congenita predominate while autoimmune adrenal insufficiency is less common (13%).

CLINICAL FEATURES

Table 1 lists the common abnormalities associated with adrenal insufficiency. *Addison disease* has insidious onset and initial clinical features are nonspecific, hence easily overlooked. Symptoms are due to deficiency of both glucocorticoids and mineralocorticoids. Glucocorticoid deficiency begins early and usually presents with anorexia, fatigue, malaise, weight loss and hypoglycemia. Signs of mineralocorticoid deficiency follow and are characterized by tachycardia, acidosis, syncope, postural dizziness, hypotension, hyponatremia and hyperkalemia. It may present with nausea, vomiting and abdominal pain (as a result of decreased gut motility) mimicking an abdominal problem. Syncope and postural dizziness mimic a neurological illness.

Pigmentation of skin and mucous membrane is a cardinal sign of Addison disease **(Figs 1A to C)**, predominantly affecting areas subjected to pressure (elbows, knuckles, palmar creases, lips, buccal, vaginal, vulval and anal mucosa, nipples and old scars). The pro-opiomelanocortin (POMC) peptides, such as melanocyte-stimulating hormone (MSH), which are secreted along with ACTH from the pituitary are responsible for the hyperpigmentation.

Clinical manifestations of *central adrenal deficiency* result from glucocorticoid deficiency alone since aldosterone production is preserved. Hyperpigmentation is not present because ACTH production is not increased.

Adrenal crisis may be a presenting feature in about half of the cases. This is precipitated by infection, trauma or surgery. Clinical features include fever, nausea, vomiting, abdominal pain, myalgia, joint pains, seizures, severe hypotension, hypovolemic shock and cardiovascular collapse.

Massive *adrenal hemorrhage* can present with shock in neonates following traumatic delivery. A flank mass is usually palpable and confirmed by abdominal ultrasonography or CT. In older children, massive adrenal hemorrhage is seen in meningococcemia. Characteristic petechial rash soon progresses into ecchymoses leading to shock, coma and death. This condition is termed as Waterhouse-Friderichsen syndrome.

INVESTIGATIONS

Diagnosis of Adrenal Insufficiency

Adrenal insufficiency is associated with low serum sodium (90%), raised serum potassium (65%) and acidosis. ECG reveals low voltage complexes and X-ray shows small heart. Associated laboratory findings include anemia, azotemia, eosinophilia and lymphocytosis (due to cortisol deficiency).

Hormonal Evaluation
- *Morning serum cortisol* In healthy people, serum cortisol concentrations are highest in early morning, values ranging from 10–20 µg/dL (275–555 nmol/L). Morning serum cortisol level (8 am) below 3 µg/dL (82 nmol/L) is diagnostic of adrenal insufficiency. Levels above 18 µg/dL (500 nmol/L) exclude Addison disease. Night time value is less than 50% of the morning value. This circadian rhythm is not well established in children below 3 years.
- *Salivary cortisol* A salivary cortisol concentration (at 8 am) of more than 5.8 µg/L (16 nmol/L) excludes adrenal insufficiency whereas a value of less than 1.8 µg/L (5 nmol/L) indicates adrenal pathology.

Table 1 Clinical manifestations and biochemical findings in adrenal insufficiency

Clinical or biochemical finding	Hormone profile
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency
Salt craving	Mineralocorticoid deficiency
Hyperpigmentation	Excess ACTH, MSH
Fever	Glucocorticoid deficiency
Low blood pressure, postural hypotension, dehydration	Mineralocorticoid deficiency, glucocorticoid deficiency
Absence of adrenarche or pubarche	Adrenal androgen deficiency
Raised serum creatinine	Mineralocorticoid deficiency
Hyponatremia	Mineralocorticoid deficiency
Hyperkalemia	Mineralocorticoid deficiency
Anemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency
Increased thyroid stimulating hormone	Glucocorticoid deficiency
Hypercalcemia	Glucocorticoid deficiency
Hypoglycemia	Glucocorticoid deficiency

Abbreviations: ACTH, adrenocorticotropic hormone; MSH, melanocyte-stimulating hormone.

Figures 1A to C A 9-year-old boy with Addison disease. Note hyperpigmentation of (A) Nails; (B) Tongue; and (C) Knuckles

Short Synacthen (ACTH) Test

This is a test of adrenal gland reserve and it assesses the response of adrenal glands to exogenous ACTH administration. An increase in serum cortisol level (above 20 µg/dL or 550 nmol/L) 1 hour after an intramuscular injection of synthetic ACTH is a normal response. Inadequate response is suggestive of adrenal insufficiency.

Low Dose (1 µg) ACTH Stimulation Test

The ACTH stimulation test is diagnostic of both primary and secondary insufficiency. This is because long-standing ACTH deficiency causes atrophy of the adrenal gland. However, some investigators have demonstrated that in central adrenal insufficiency of short duration when the adrenal gland is not yet atrophied, the full dose ACTH stimulation test will not give an abnormal result. It has been shown in many studies that a modification of short ACTH test, in which physiological dose of 1 µg of ACTH is used, is useful in the investigation of central adrenal insufficiency and also to assess adrenal recovery from glucocorticoid suppression.

Plasma ACTH Measurement

In adults and older children, normal 8 am value never exceeds 50 pg/mL; 8 pm values are usually undetectable. In the setting of corticosteroid insufficiency, raised plasma ACTH level is suggestive of Addison disease while a low level is indicative of secondary adrenal insufficiency. Samples should be drawn into a plastic syringe containing heparin or ethylene diamine tetra-acetic acid (EDTA) and quickly transported in plastic tubes on ice as ACTH adheres to glass and is quickly inactivated.

Plasma Renin Activity

Plasma renin activity (PRA) is an immunoassay of the amount of angiotensin I formed per mL of serum per hour at 37°C in the presence of excess amount of angiotensinogen. It is an index of mineralocorticoid activity. Primary adrenal insufficiency is characterized by high PRA. Plasma concentration of renin and aldosterone is not altered in central adrenal insufficiency, hence PRA remains normal.

Table 2 provides the mean glucocorticoid and mineralocorticoid concentrations in children.

Table 2 Mean glucocorticoid and mineralocorticoid concentrations in children

	Cortisol [nmol/L (µg/dL)]	Aldosterone (nmol/L)	Plasma renin activity (µg/L/h)
Cord blood	360 (13)	2.4 (87 ng/dL)	50
Premature	180 (6.5)	2.8 (101 ng/dL)	222
Newborns	140 (5)	2.6 (94 ng/dL)	58
Infants	250 (14.2)	0.8 (29 ng/dL)	33
Children (8 am)			
1–2 years	110–150 (4–20)	0.8	15
2–10 years	As adults	0.3–0.8	8.3
10–15 years	As adults	0.1–0.6	3.3
Adults			
8 am	280–550 (10.4–20)	0.2–0.4	2.8–4
4 pm	140–280 (5–10)		

Adapted from Sperling MA, 2008.
Note: To convert cortisol to µg/dL, multiply by 0.0363; two values of aldosterone and plasma renin activity indicate supine and upright values.

Diagnosis of Etiology (Flow chart 1)

Tuberculosis

A positive contact history is an important clue, but tuberculin test may not be positive in many cases. CT abdomen showing calcification of adrenal gland is suggestive.

Autoimmune Addison Disease

Presence of another autoimmune disorder (e.g., vitiligo) is a pointer toward autoimmune Addison disease. Both adrenal cortical autoantibodies and 21-hydroxylase antibodies should be measured. These children should be investigated for other features of autoimmune polyendocrinopathy syndromes.

X-linked Adrenoleukodystrophy

In all boys, if adrenal antibodies are negative, plasma very long-chain fatty acids (VLCFA) levels must be done to rule out adrenoleukodystrophy

Allgrove Syndrome

Schirmer test can be performed to look for conjunctival dryness.

MANAGEMENT

Treatment of primary adrenal insufficiency requires replacement of both glucocorticoids and mineralocorticoids. Adrenal insufficiency is a life-threatening disease; hence, treatment should be initiated at the earliest. Replacement therapy is usually lifelong. Hence, proper education of the patients as well as their families is of paramount importance for the success of the treatment. Tuberculosis and HIV infection need specific treatment along with corticosteroid replacement therapy.

Glucocorticoid Replacement

Daily production of cortisol ranges from 6–8 mg/m^2. Glucocorticoid replacement should mimic the normal circadian rhythm. Hydrocortisone is the most physiological option for glucocorticoid replacement. The recommended daily dose is 10–12 mg/m^2. To mimic the circadian secretion of cortisol, hydrocortisone can be given in three doses with one-half to two-thirds of the total dose in the morning. Long-acting synthetic derivatives like prednisolone,

Flow chart 1: Algorithm for etiological work up of adrenal insufficiency
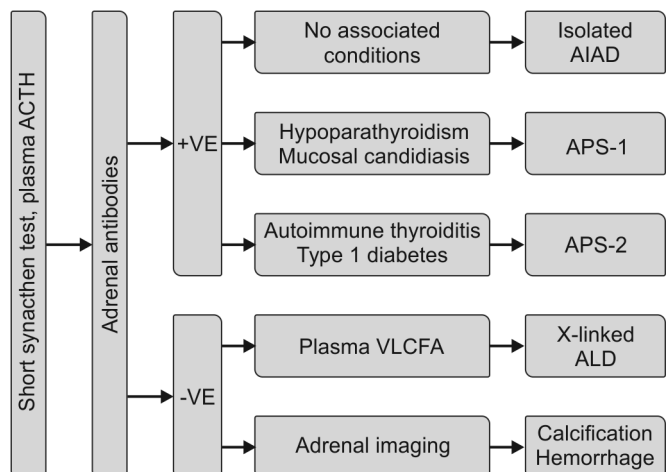
Abbreviations: ACTH, adrenocorticotropic hormone; VLCFA, very long-chain fatty acid; ALD, adrenoleukodystrophy; APS-1, autoimmune polyglandular (polyendocrinopathy) syndromes type 1; APS-2, autoimmune polyglandular (polyendocrinopathy) syndromes type 2; AIAD, autoimmune Addison disease.

dexamethasone and betamethasone are not preferred because of higher incidence of toxicity including linear growth failure.

Stress Dosing

During minor illness, dose of hydrocortisone should be increased to 2–3 times of the replacement dose to avoid an adrenal crisis. During major illnesses and during surgery, dose should be 5–10 times of the replacement dose. Children receiving treatment with drugs which increase hepatic metabolism of glucocorticoids (e.g., rifampicin, phenobarbitone and phenytoin) need a higher dose of hydrocortisone.

Mineralocorticoid Replacement

Mineralocorticoid replacement is required only in primary adrenal insufficiency since renin-angiotensin system is intact in secondary adrenal insufficiency. Synthetic mineralocorticoid 9α-fluorohydrocortisone (fludrocortisone) in a dose of 0.05–0.2 mg daily (in the morning) is the preferred drug.

Salt Supplementation

Since breastmilk and infant formula contain very low amount of salt, infants require salt supplementation (1–2 g/day), particularly when they have serum electrolyte abnormalities and elevated PRA levels. When they start eating complementary food, salt supplementation can be stopped.

Treatment of Adrenal Crisis

In a normal child, adrenal glucocorticoid production can increase up to six times during stressful situations. Adrenal crisis occurs if the adrenal production is not matching with increased demand during stress. The most common precipitating events in children are fever and diarrhea. Other major causes include trauma and surgery. **Box 2** describes the clinical and laboratory features of adrenal crisis.

Emergency management consists of treatment of dehydration and hypotension, electrolyte imbalance and cortisol deficiency. Hydrocortisone is given as IV bolus of 25–50 mg/m^2 initially followed by 50–75 mg/m^2 added to the 24-hour maintenance fluid solution (total daily dose is 100 mg/m^2). There is no need to supplement mineralocorticoid at this stage since high dose of hydrocortisone has adequate mineralocorticoid activity. Clinical improvement is usually obvious within 6 hours of glucocorticoid administration. **Box 3** summarizes the treatment of acute adrenal insufficiency.

Children who receive glucocorticoid therapy for more than 1 month have an unresponsive HPA axis. As a result, they require additional glucocorticoids during stress similar to children with CAH. These children should be followed up at least 1 in 4–6 months which include:
- Monitoring of height velocity, weight, body mass index (BMI) are mandatory in each visit.
- Check whether glucocorticoid or mineralocorticoid replacement is adequate.
- Involvement of other endocrine glands should be checked annually in autoimmune adrenal insufficiency. This includes

BOX 2 Clinical and laboratory features of adrenal crisis

- Dehydration, hypotension, shock
- Anorexia, nausea, vomiting and weight loss
- Abdominal pain, acute abdomen
- Hypoglycemia
- Fever
- Hyponatremia, hyperkalemia, azotemia, eosinophilia
- Hyperpigmentation.

BOX 3 Treatment of acute adrenal insufficiency

- Monitor ABC, establish an IV line
- Draw blood for measuring electrolytes, glucose, RFT, CBC, culture, basal cortisol and ACTH
- Start 20 mL/kg of 0.9% saline with 5% dextrose in the first hour
- Inject hydrocortisone @ 25 mg/m^2 IV into the fluid
- Reassess after first hour, repeat the bolus if still in shock
- Continue normal saline with 5% dextrose as maintenance fluid for next 24–48 hours
- Inject hydrocortisone at 100 mg/m^2/day IV in four divided doses
- Search for and treat the possible infectious cause precipitating the illness
- Perform the short synacthen test to confirm the diagnosis
- Taper glucocorticoids to maintenance dose over 1–3 days
- Start oral fludrocortisone 0.1 mg when saline infusion is stopped
- Investigate for the etiology.

Abbreviations: ABC, airway, breathing, circulation; RFT, renal function test; CBC, complete blood count; ACTH, adrenocorticotropic hormone; IV, intravenous.

thyroid function tests, fasting blood sugar and complete blood counts.
- Should reinforce patient education regarding stress dose.

A promising advance in the management of Addison disease is development of a modified-release hydrocortisone tablet that can mimic the circadian rhythm of endogenous cortisol production.

AUTOIMMUNE ADRENALITIS

This is a common cause of primary adrenal insufficiency affecting adults between 25 years and 50 years, mostly females (70%). It is less common in children and boys predominate (75%). It may present as isolated adrenal insufficiency (40%) or as a part of an autoimmune polyendocrinopathy syndrome (60%). Autoimmune Addison disease is characterized by destruction of adrenal cortex by cell-mediated immune mechanisms. Antibodies against steroid 21-hydroxylase are detected in 85% of patients. Antibodies against steroid 17α-hydroxylase and cholesterol side-chain cleavage enzyme have also been identified in some children.

AUTOIMMUNE POLYGLANDULAR (POLYENDOCRINOPATHY) SYNDROMES

Autoimmune polyglandular (polyendocrinopathy) syndromes (APS) are associated with multiple endocrine dysfunctions with an autoimmune etiology. Autoimmune polyglandular (polyendocrinopathy) syndrome type 1 (APS-1) is more commonly seen in childhood and adolescence and autoimmune polyglandular (polyendocrinopathy) syndrome type 2 (APS-2) is generally present in adulthood. **Table 3** lists the common features of APS seen in children.

Autoimmune Polyglandular (Polyendocrinopathy) Syndrome Type 1

Autoimmune polyglandular (polyendocrinopathy) syndrome type 1, also known as polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), is usually seen in childhood. Two of the three cardinal components (autoimmune adrenal failure, chronic mucocutaneous candidiasis and autoimmune hypoparathyroidism) are required for clinical diagnosis. The classic triad develops in 60% of the affected children. The gene defective in APS is located on chromosome 21q22.3. It is named as autoimmune regulator (AIRE) gene. Pathogenesis of APS-1 is unclear, but autoimmunity is the underlying event. Autoantibodies directed against interferons, mainly IFN-α and IFN-ω, have 100% prevalence in children with APS-1 and appear to be disease specific.

Table 3 Autoimmune polyglandular syndromes

Characteristics	APS type 1	APS type 2
Age group (onset)	Infancy and early childhood	Late childhood and adolescence
Mode of inheritance	Autosomal recessive	Polygenic
Gender	No predilection	Common in females
Gene abnormality	*AIRE* gene, no HLA association	HLA association
Mucocutaneous candidiasis	Very common (75–100%)	None
Ectodermal dysplasia	Common (75%)	None
Hypoparathyroidism	Very common (75–90%)	None
Addison disease	Very common (60–90%)	Very common (70–100%)
Type 1 diabetes	Rare (10%)	Common (50%)
Autoimmune thyroid disease	Rare (20%)	Common (70%)
Pernicious anemia	Rare	Rare
Gonadal failure	Common in females	Rare
Autoimmune hepatitis	Rare	Rare

Abbreviations: APS, autoimmune polyglandular (polyendocrinopathy) syndrome; AIRE, autoimmune regulatory; HLA, human leukocyte antigens.

Major Manifestations

- *Mucocutaneous candidiasis* It is the first and the most common (75–100%) manifestation of APS-1. It usually begins at 2 years of life. Oral candidiasis is most common, but it can also affect esophagus, intestine, vaginal mucosa, nails and skin.
- *Hypoparathyroidism* It is usually the first endocrine manifestation with peak incidence between 5 years and 10 years. It occurs in 75–90% of all patients, but majority are asymptomatic. In symptomatic children, they present with tetany, laryngospasm and seizures.
- *Autoimmune adrenal failure.* It is the third cardinal feature and usually present by age 10–15 years. Autoimmune damage occurs gradually, hence full-blown Addison disease manifests years later.

Minor Manifestations

- *Autoimmune endocrinopathies*: Primary hypogonadism (the most common, 25–50%), autoimmune thyroiditis and type 1 diabetes.
- *Gastrointestinal manifestations*: Chronic atrophic gastritis presenting as pernicious anemia or iron deficiency anemia; malabsorption, presenting as chronic diarrhea or as steatorrhea and exocrine pancreatic deficiency; cholelithiasis and chronic active hepatitis.
- *Skin, nails and teeth*: Vitiligo, alopecia, chronic urticaria, ectodermal dystrophy of nails and enamel, and pitted nails are important clues toward diagnosis. Enamel hypoplasia is seen half of all affected children, but deciduous teeth are never affected.

Treatment

Different endocrine disorders are managed by conventional hormonal replacement. Mucocutaneous candidiasis is managed by oral or systemic antifungal drugs, good dental and oral hygiene. For children with hypoparathyroidism, vitamin D analogs are given so as to keep the serum calcium level around the lower limit of normal. Adrenal insufficiency is treated with hydrocortisone.

Autoimmune Polyglandular (Polyendocrinopathy) Syndrome Type 2

Autoimmune polyglandular (polyendocrinopathy) syndrome type 2 is characterized by primary adrenal insufficiency with either autoimmune thyroiditis or type 1 diabetes in the same individual. The association of autoimmune Addison disease and autoimmune thyroid disease is called Schmidt syndrome, and the association of Addison disease with type 1 diabetes is named as Carpenter syndrome. This condition is usually seen in young adults, very rarely in children. Adrenal insufficiency is seen in all affected children and is usually the first clinical presentation. Autoimmune thyroiditis is the next common (70–90%) endocrinopathy and type 1 diabetes is the least common (20–50%) disorder. Primary hypogonadism is a common minor manifestation. Other manifestations include vitiligo, alopecia, autoimmune hepatitis and malabsorption syndrome. APS-2 is a multifactorial disease. Inheritance is autosomal dominant with incomplete penetrance. Three genes that have shown consistent association with APS-2 are *HLA, CTLA4* and *PTPN 22.* Management mainly consists of treatment of individual diseases.

Autoimmune Polyglandular (Polyendocrinopathy) Syndrome Type 3

Autoimmune polyglandular (polyendocrinopathy) syndrome type 3 (APS-3) is the association between autoimmune thyroid disease and autoimmune diseases other than Addison disease. Some consider this entity as a variant of APS-2.

X-LINKED ADRENOLEUKODYSTROPHY

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder (also see Chapter 42.26). It is characterized by mutations in *ABCD1* gene located in the X chromosome (xq28) which encodes the peroxisomal membrane protein [adrenoleukodystrophy protein (ALDP)] which is involved in the transmembrane transport of very VLCFA from the cytosol into the peroxisome. The key biochemical defect involves the impaired function of peroxisomal lignoceroyl CoA ligase, the enzyme that catalyzes the formation of the CoA derivative of VLCFA. Reduced level of ALDP results in elevated levels of VLCFA in blood and tissues.

Clinical Features

Abnormal deposition of VLCFA (carbon chain length 24 or more) in various tissues including white matter of brain, spinal cord and adrenal cortex produces the symptoms. Adrenal insufficiency is a common presenting feature, which may occur years before neurological manifestations. Childhood cerebral ALD usually presents in school going children (7–8 years). The onset is insidious with defects in cognitive abilities resulting in poor school performance. As the disease progress, auditory impairment, decreased visual acuity, hemiparesis, spastic quadriplegia, cerebellar ataxia and seizures set in. Death usually occurs within 2–3 years after the diagnosis.

Diagnosis

Elevated levels of VLCFA are confirmatory. All male children with features of primary adrenal insufficiency must be investigated for adrenoleukodystrophy. Brain MRI may show abnormal signal intensities in the corpus callosum and parieto-occipital region. MRI findings can be demonstrated very early in the disease.

Management and Follow-up

Children with ALD should be followed-up for early detection of clinical features of adrenal insufficiency or cerebral ALD. Steroid replacement therapy can be initiated if they show features of adrenal deficiency. Allogeneic hematopoietic stem cell transplantation (HCT) remains the only therapeutic intervention that can arrest the progression of cerebral demyelination in X-linked ALD. Monounsaturated fatty acids which block the synthesis of saturated VLCA, such as Lorenzo's oil (4:1 mixture of oleic acid and erucic acid) combined with a dietary regimen with low VLCFA, is recommended for neurologically asymptomatic boys who have a normal brain MRI and are younger than 8-year-old boy.

CONGENITAL ADRENAL HYPERPLASIA

In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia. The most common form is classic 21-hydroxylase deficiency. Other important forms are deficiency of 11β-hydroxylase; 17α-hydroxylase; 17,20-lyase; 3β-hydroxysteroid dehydrogenase and P450 oxidoreductase (see Chapter 44.15 for details).

CONGENITAL ADRENAL HYPOPLASIA

Congenital adrenal hypoplasia is a rare disease. The most common inheritance pattern is X-linked recessive and hence the disease is more commonly seen in boys. X-linked form is caused by a mutation or deletion of the *DAX1* gene (dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region of the X chromosome, also called the *NR0B1* gene) on the X chromosome.

Clinical Features

These usually present in the neonatal period with features of adrenal insufficiency with dehydration, hyponatremia, hyperkalemia, hypoglycemia and shock. Hyperpigmentation is a common finding. Growth failure and short stature is a usual finding. Hypogonadotropic hypogonadism is a common late manifestation. Since the gene locus is located near to Duchenne muscular dystrophy (DMD) locus in X chromosome, some children may also develop muscular dystrophy.

Diagnosis

A low serum cortisol in the presence of elevated ACTH is suggestive of adrenal insufficiency. ACTH stimulation test can confirm the diagnosis of insufficiency. Serum 17-hydroxyprogesterone levels will be normal. Plasma VLCFA level and autoimmune adrenal antibodies are not elevated. Karyotype, fluorescent in situ hybridization (FISH) or microarray analysis helps to detect the gene deletion involving *DAX1*. Muscle biopsy is indicated to rule out the possibility of DMD. Gonadotropin (LH, FSH) estimation is needed if they present with features of delayed puberty.

Treatment

Adrenal insufficiency is treated with glucocorticoid and mineralo-corticoid replacement. Hypogonadotropic hypogonadism needs testosterone administration.

IN A NUTSHELL

1. Addison disease has insidious onset and initial clinical features are nonspecific, hence easily overlooked.
2. Hyperpigmentation of skin and mucous membrane is a cardinal sign of Addison disease.
3. Adrenal insufficiency is associated with hyponatremia, hyperkalemia and acidosis due to mineralocorticoid deficiency.
4. Estimation of morning plasma cortisol followed by a short ACTH stimulation test helps to confirm the diagnosis of adrenal insufficiency.
5. Treatment of primary adrenal insufficiency requires replacement of both glucocorticoids and mineralocorticoids. Hydrocortisone is the most physiological option for glucocorticoid replacement.
6. Emergency management consists of treatment of dehydration and hypotension, electrolyte imbalance and steroid therapy.
7. APS-1 is characterized by autoimmune adrenal failure, chronic mucocutaneous candidiasis and autoimmune hypoparathyroidism.
8. APS-2 is characterized by primary adrenal insufficiency with either autoimmune thyroiditis or type 1 diabetes in the same individual.

MORE ON THIS TOPIC

Brandão Neto RA, de Carvalho JF. Diagnosis and classification of Addison's disease. Autoimmun Rev. 2014;13:408-11.

Brook CGD, Mehul T. The adrenal gland. In: Dattani MT. Handbook of Clinical Pediatric Endocrinology. 2nd ed. West Sussex: Wiley Blackwell; 2012. pp. 151-74.

Colaco P. Adrenal insufficiency. In: Desai MP, Menon PSN, Bhatia V. Pediatric Endocrine Disorders. 3rd ed. Hyderabad: University Press; 2014. pp. 248-54.

Cutolo M. Autoimmune polyendocrine syndromes. Autoimmun Rev. 2014; 13:85-9.

Hahner S, Allolio B. Therapeutic management of adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2009;23:167-79.

Husebye E, Løvås K, Pathogenesis of primary adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2009;23:147-57.

Migeon CJ, Lanes RL. Adrenal cortex: Hypo- and Hyperfunction. In: Lifshits F. Pediatric Endocrinology. 4th ed. New York: Marcel Decker; 2008. pp. 147-92.

Miller WM, Achermann JC, Fluck CE. Adrenal cortex and its disorders. In: Sperling MA. Pediatric Endocrinology. 3rd ed. Philadelphia: Elsevier Saunders; 2008. pp. 444-511.

Owen CJ, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. Endocrinol Metab Clin North Am. 2009;38:419-36.

Stewart PM, Krone NP. Glucocorticoid deficiency. In: Melmed S, Polonski KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology. 12th ed. Philadelphia: Elsevier Saunders; 2011; pp. 515-23.

Chapter 44.17
Cushing Syndrome
Maha Elhassan, Michael A Wood

Obesity in children has become a worldwide problem. Clinicians are often faced with the dilemma of which children to evaluate for a hormonal cause. Cushing syndrome is a rare but treatable cause of childhood obesity and results from prolonged exposure to supraphysiologic levels of glucocorticoids (cortisol, prednisone, dexamethasone, inhaled corticosteroids, and others). Making the diagnosis of Cushing syndrome is important not only because of its potential curability but also glucocorticoid excess can have permanent effects on growth and development.

EPIDEMIOLOGY

In both the developing and developed world, the most common cause for Cushing syndrome in children is exposure to exogenous glucocorticoids [or adrenocorticotropic hormone (ACTH)] at supraphysiologic levels for conditions such as cancer, inflammatory diseases, post-transplant and asthma. It can also occur when inhaled corticosteroids are taken for asthma or with topical steroid therapy. Clinicians must consider this possibility when their patients are on prolonged steroid therapy.

Endogenous Cushing syndrome is seen rarely (< 1/1,000,000) in children. Boys are more affected than girls in the prepubertal period, whereas girls and boys seem to be equally affected during puberty. In postpubertal adolescents and adults, women are affected more often than men.

ETIOLOGY

The most common etiology of endogenous Cushing syndrome in children varies by age. In children age 5 years or less, a primary adrenal cause is most common. In the first few months of life, Cushing syndrome is most commonly caused by adrenal hyperplasia due to the McCune-Albright syndrome.

In older infants and preschool-aged children, adrenal cortical tumors (ACT) account for more than 80% of patients. These tumors are rare in children with a worldwide annual incidence of 0.3/1,000,000 less than age 15 years. Benign adrenal adenomas are most common and often lead to symptoms of glucocorticoid excess, and many cause hypertension. They are difficult to distinguish pathologically from adrenal carcinoma which may present with Cushing syndrome, rapid virilization or with a palpable mass and no symptoms of adrenal hormone hypersecretion (20–40%). Adrenal carcinomas tend to occur in young children; the median age of diagnosis is 3.2 years and 60% are younger than 4 years. ACT can be associated with numerous tumor syndromes including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, multiple endocrine neoplasia type 1 and hemihypertrophy syndrome. Other adrenal causes for Cushing syndrome are rarer and include primary pigmented nodular adrenocortical disease (PPNAD) with Carney complex (multiple neoplasia syndrome) and macronodular adrenal hyperplasia.

In children older than age 5 years and adults, a benign ACTH-secreting pituitary adenoma is the most likely cause of Cushing syndrome. This specific diagnosis is termed Cushing disease. Another ACTH-dependent cause, ectopic ACTH syndrome, is extremely rare in children. ACT and Cushing disease account for more than 90% of endogenous Cushing syndrome.

PATHOGENESIS OR PATHOPHYSIOLOGY

Cortisol is a steroid hormone produced in the zona fasciculata of the adrenal cortex under strict physiologic control with a classic endocrine feedback loop involving ACTH and corticotropin-releasing hormone (CRH) **(Fig. 1)**. Its production is regulated by ACTH, a 39 amino acid pituitary peptide hormone created after cleavage from pro-opiomelanocortin (POMC), a 241 amino acid precursor protein. ACTH secretion is regulated by CRH, a peptide from the paraventricular nucleus of the hypothalamus. CRH is released into the pituitary portal circulation and binds to G-protein-coupled receptors on pituitary corticotropes, activating adenylyl cyclase [increased cyclic adenosine monophosphate (cAMP)] leading to ACTH secretion. Arginine vasopressin (AVP) is contained in the same hypothalamic neurons and synergistically increases the CRH effect on ACTH secretion.

Once secreted by the pituitary, ACTH circulates to the adrenal cortex where it binds to cells in the zona fasciculata by the G protein-coupled, melanocortin-2 receptor (MC2R). This also
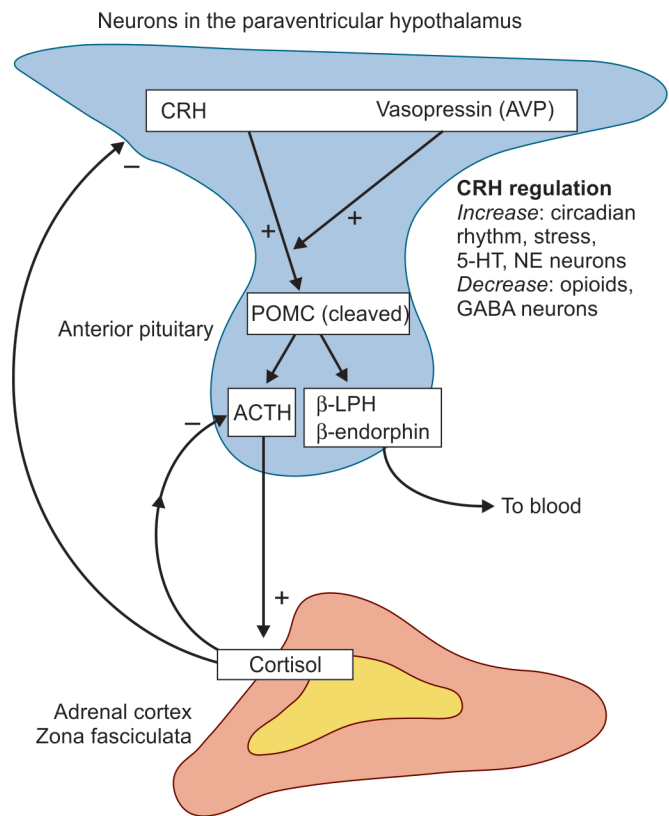
Figure 1 The hypothalamic-pituitary-adrenal axis. The normal circadian rhythm and stress lead to hypothalamic CRH release into the hypothalamic-pituitary portal circulation. AVP is contained in the same neurons, and augments CRH mediated ACTH secretion. At the level of the hypothalamus, serotonergic and norepinephrine neurons stimulate CRH release, whereas GABA and endogenous opioids inhibit CRH release. Within the corticotropes of the anterior pituitary, CRH stimulates production of POMC which is cleaved to ACTH, β-LPH and β-endorphin. ACTH travels via the systemic circulation to the adrenal cortex, leading to synthesis and release of cortisol. Cortisol levels circulate back to the hypothalamus to inhibit CRH and to the pituitary to inhibit ACTH release in a classic endocrine feedback loop
Abbreviations: ACTH, adrenocorticotropic hormone; GABA, γ-aminobutyric acid; CRH, corticotropin-releasing hormone; POMC, pro-opiomelanocortin; β-LPH, β-lipotropin; 5-HT, 5-hydroxytryptamine; NE, norepinephrine; AVP, arginine vasopressin.

increases intracellular cAMP and the activity of several enzymes critical for steroidogenesis. The net effect is an increase in cortisol secretion, largely due to de novo synthesis from intracellular cholesterol.

In addition to enhancing cortisol production, ACTH increases adrenal blood flow and adrenal growth. Chronically, elevated levels of any glucocorticoid will cause suppression of CRH and ACTH, leading to adrenal atrophy. After adrenalectomy for a unilateral hyperfunctioning adrenal tumor, the contralateral atrophied adrenal and hypothalamic-pituitary-adrenal (HPA) axis may take many months to recover. After successful resection of an ACTH-producing pituitary adenoma, hypothalamic CRH will remain suppressed for months; low ACTH levels will lead to adrenal atrophy within a few weeks.

The importance of the HPA axis in human physiology and the stress response has been extensively studied. Cortisol is secreted in response to stress (physical and emotional) and can remain elevated with chronic stress. Beginning in infancy, it is produced in a circadian rhythm with the highest levels around 8 am and lowest levels in the evening. Numerous stress-related disorders including depression, alcoholism, malnutrition and panic disorders are accompanied by increased cortisol levels.

Under normal circumstances, cortisol is important in the physiologic response to fasting and hypoglycemia, enhancing gluconeogenesis and glycogenolysis with the net effect of increasing the blood sugar. It is also important in the maintenance of blood pressure and normal cardiovascular function by enhancing sensitivity to catecholamines. In the absence of cortisol, vasodilation and hypotension can occur.

All glucocorticoids (including prednisolone and dexamethasone and others) exhibit the above effects. This class of agents has potent anti-inflammatory effects, reducing cytokine and histamine secretion and stabilizing cell membranes and is used therapeutically for this purpose. Cortisol can, unlike prednisone and dexamethasone, bind to the mineralocorticoid receptor (MCR) leading to renal sodium retention and potassium excretion. Under normal conditions, the renal enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) converts much of the incoming cortisol to cortisone which is unable to bind to the MCR. The net effect is decreased intrarenal cortisol available to bind to the MCR. In some forms of endogenous Cushing syndrome, hypertension occurs both due to excessive cortisol production and MCR binding, but also due to excessive aldosterone production.

Glucocorticoids suppress linear growth by increasing hypothalamic secretion of somatostatin and decreasing growth hormone (GH) secretion and insulin-like growth factor-1 (IGF-1) production. In addition, they directly inhibit epiphyseal growth. Excessive glucocorticoid causes muscle wasting and decreased bone density. Effects on the skeleton and calcium metabolism include: (a) decreased bone formation and inhibition of osteoblast function, (b) increased bone resorption and stimulation of osteoclast proliferation, and (c) decreased intestinal calcium absorption.

CLINICAL FEATURES

The classic description of Cushing syndrome in adults includes a round (*moon*) facies, central obesity, thin limbs (muscle wasting), hirsutism, facial flushing, wide, violaceous abdominal striae, fat deposition on the upper back (buffalo hump) and hypertension. The presentation of the child with Cushing syndrome usually includes suboptimal height gain with accelerating weight gain and increasing body mass index (BMI) **(Fig. 2)**. In some patients, the obesity may appear generalized rather than central and the distinguishing feature is poor linear growth as children with exogenous obesity grow rapidly. Other clinical findings of Cushing

syndrome in children are more variable. In a series of 59 children with Cushing syndrome evaluated at the National Institutes of Health (NIH) **(Table 1)**, only excessive weight gain and growth retardation were seen in greater than 80% of patients.

Other signs and symptoms of Cushing syndrome in children include fatigue, headaches, amenorrhea, delayed or advanced sexual development, weakness and osteopenia. Bone age delay has been variably described in published studies (11–50%) but a negative effect on final adult height is typical. Advanced bone age is uncommon. In a pubertal-aged child with Cushing syndrome, adrenarche (pubic hair, axillary hair, acne) is often more advanced than gonadarche (breast development in girls, testicular enlargement in boys) and can be a clinical clue. Skin manifestations may include wide violaceous striae and easy bruising due to steroid-induced dermal atrophy and fragility. Acanthosis nigricans is a consequence of insulin resistance. Psychiatric disturbances include compulsive behavior (40%) or emotional liability (30%) and less commonly depression.

As a result of the variable presentation, the diagnosis of Cushing syndrome in children can be delayed if height is not monitored carefully. In children with an adrenal adenoma or pituitary adenoma, Cushing syndrome is the most common presentation, although virilization can be seen in the former. In the case of adrenal carcinoma, the presentation can include Cushing syndrome or a rapid virilizing course with pubic hair, acne or phallus enlargement (clitoris or penis).

DIFFERENTIAL DIAGNOSIS

In the child with increasing weight gain and slow linear growth, the main considerations in addition to Cushing syndrome include hypothyroidism, hypopituitarism (i.e., craniopharyngioma) and various syndromes (Prader-Willi syndrome, pseudohypoparathyroidism). Pseudo-Cushing syndrome (some of the clinical and biochemical features of Cushing syndrome) is extremely rare in children and most commonly seen in alcoholic adults. It has been rarely described in infants exposed to alcohol in breastmilk. In other hypercortisolemic states (physical and emotional stress, depression, chronic severe obesity, excessive exercise, poor diabetes control, anorexia, narcotic withdrawal, anxiety and malnutrition), elevated urinary free cortisol is rarely accompanied by features suggestive of Cushing syndrome.

APPROACH TO DIAGNOSIS (FIG. 3)

Appropriate therapy in Cushing syndrome depends on an accurate diagnosis. The history and physical examinations, including review of growth data and a very careful history of drug intake including from alternative systems of medicine as a cause of exogenous Cushing syndrome, are important to guide the laboratory evaluation. Initial screening should include thyroid function testing [free thyroxine (T4) and thyroid-stimulating hormone (TSH)] to exclude hypothyroidism, a serum chemistry panel to assess the calcium, glucose and electrolytes and androgens [dehydroepiandrosterone sulfate (DHEAS) and testosterone] if virilization is present. Extreme elevation of the DHEAS can indicate possible adrenal carcinoma. If neurologic symptoms (especially headaches) are present, pituitary screening tests [prolactin, IGF-1, luteinizing hormone (LH), follicle stimulating hormone (FSH) and morning cortisol to rule out panhypopituitarism] are indicated.

Upon suspicion of Cushing syndrome, outpatient screening tests to document hypercortisolism are indicated. Imaging is performed only after a diagnosis of Cushing syndrome has been confirmed. This is critical since nonfunctioning incidental tumors can be found in the adrenal or pituitary, leading to ineffective surgery with improper diagnosis.
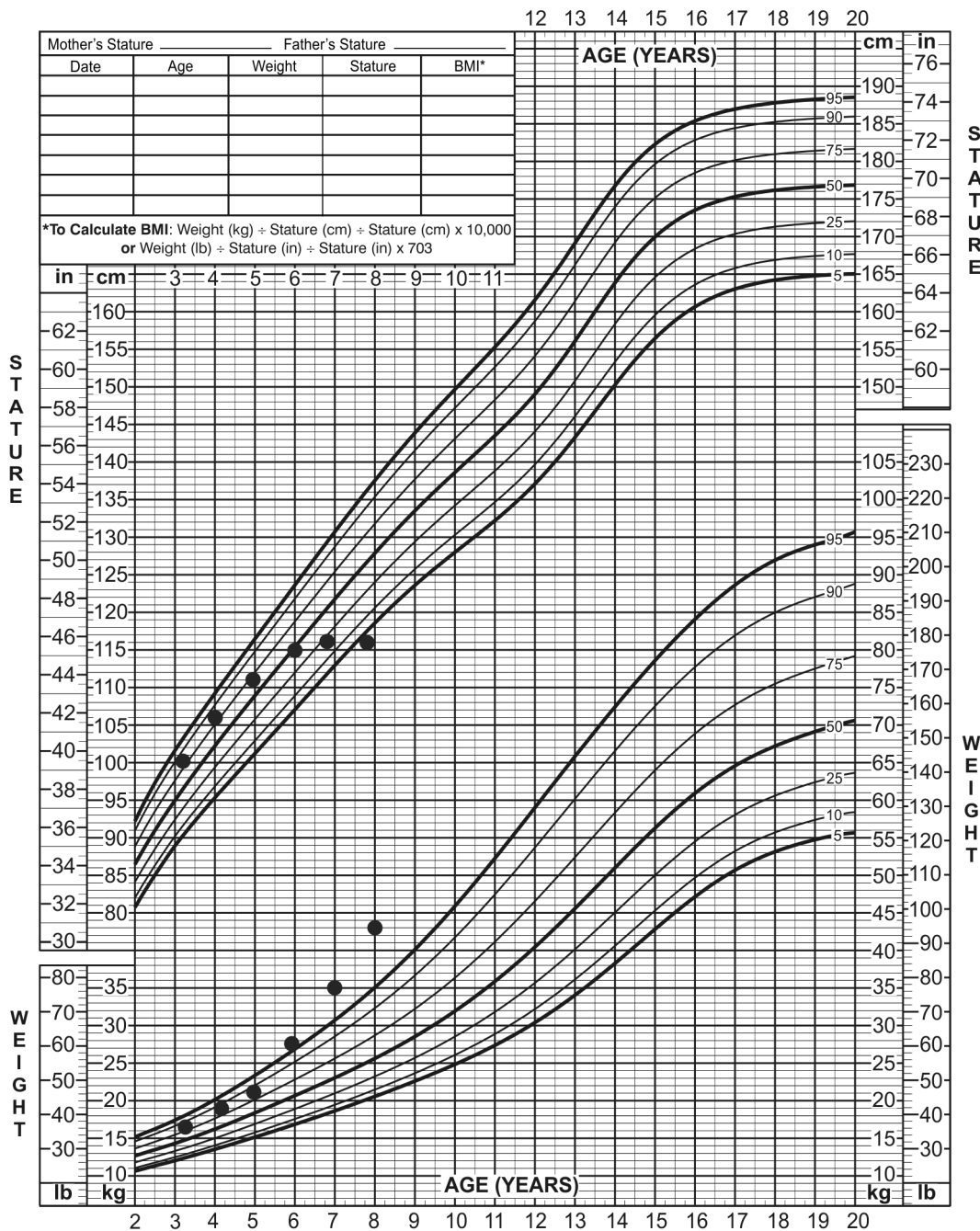
Figure 2 The typical growth chart of a child with Cushing syndrome. Note the dramatic slowing of linear growth and the increased weight gain

Screening Tests

The most common screening test utilized is the *24-hour urinary free cortisol (UFC)* with a 24-hour urine creatinine level done to ensure an adequate collection. A normal 24-hour UFC is less than 70 μg/m^2/day. Levels greater than four times the normal indicate Cushing syndrome. Repeat collections are suggested. Falsely elevated UFC may be seen in pseudo-Cushing syndrome

described above and with high fluid intake. Falsely low UFC can be seen with low urine volume, renal insufficiency and with an inadequate urine collection. Exogenous Cushing syndrome will be associated with low UFC, low 8 am cortisol and a low cortisol after a stimulation test.

Another common screening test is the *low-dose overnight dexamethasone suppression test* (DST). In most cases of Cushing

Table 1 Frequency of signs and symptoms in the NIH series of 59 children with Cushing syndrome

Symptom or sign	Percentage of children with symptom or sign
Weight gain	90
Growth retardation	83
Menstrual irregularity, girls > 15 years	78
Hirsutism in girls	78
Obesity (BMI > 85th percentile)	75
Violaceous skin striae	61
Acne	47
Hypertension	47
Fatigue or weakness	44
Early secondary sexual development	38
Bruising	25
Mental changes	19
Hyperpigmentation	14
Muscle weakness	12
Acanthosis nigricans	12
Delayed bone age	11
Advanced bone age	8
Sleep disturbance	8
Hypercalcemia	7
Alkalosis	7
Other (delayed puberty, hypokalemia, SCFE)	< 5

Abbreviations: NIH, National Institutes of Health; BMI, body mass index; SCFE, slipped capital femoral epiphysis.

syndrome, low-dose dexamethasone will not suppress the HPA axis. This test involves administering 15 μg/kg (maximum dose 1 mg) of dexamethasone orally at 11 pm. At 8 am the next morning, the serum cortisol should be less than 1.8 μg/dL; a level greater than 10 μg/dL is highly suggestive of Cushing syndrome. This test has a low false-negative rate but a higher false positive rate (15–25%).

If both the UFC and DST are normal, the likelihood of Cushing syndrome is low. However, 5–10% of patients may have intermittent or periodic excessive cortisol secretion. If episodic Cushing syndrome is suspected, continued follow-up and periodic testings are required.

A final screening test for Cushing syndrome involves *evening cortisol sampling* as the loss of diurnal variation is typical. A cortisol measurement at midnight from an indwelling venous catheter is obtained. A value greater than 2 μg/dL is suggestive of Cushing syndrome and a level of greater than 4.4 μg/dL is greater than 99% sensitive and 100% specific for Cushing syndrome. After the screening tests, if the diagnosis of Cushing syndrome is likely, definitive testing to localize the lesion is performed often with assistance from a pediatric endocrinologist.

Localization and Characterization
Investigations are performed to distinguish ACTH-dependent from ACTH-independent disease. A *spot morning plasma ACTH* is measured. A level of 29 pg/mL or greater in a child with Cushing syndrome has a sensitivity of 70% for identifying an ACTH-dependent form. Most patients with ACT have completely suppressed ACTH levels. Additional testing is also performed to distinguish between Cushing disease (usually suppressible with high dose dexamethasone) from the non-suppressible causes of Cushing syndrome (adrenal adenoma, adrenal carcinoma, ectopic ACTH syndrome, others).

The standard *low dose and high dose dexamethasone suppression test (LDDST, HDDST)* are often done sequentially in the hospital setting. Two days of baseline testing is followed by 2 days of low dose dexamethasone (20 μg/kg/day, maximum 2 mg/24 hour,

divided every 6 hours) and 2 days of high dose dexamethasone. (80 μg/kg/day, maximum dose 8 mg/24 hour, divided every 6 hours) 24-hour UFC is collected daily (with creatinine levels) and 8 am and 8 pm cortisol and ACTH levels are obtained on each of the 6 days. Normal results include an 8 am cortisol after LDDST and HDDST of less than 5 μg/dL, ACTH less than 20 pg/mL as well as a UFC less than 10% of baseline. Cushing disease is most likely when the levels are suppressed on the HDDST, but not the LDDST. In most other diagnoses of Cushing syndrome (primary adrenal source, ectopic ACTH), the LDDST and HDDST do not cause suppression. In this situation, ACTH levels help distinguish between the two.

CRH stimulation test may also be used for the differentiation of Cushing disease from ectopic ACTH syndrome and/or adrenal lesions. In this test, 1 μg/kg of CRH is injected, and cortisol and ACTH levels are monitored. 85% of patients with Cushing disease respond to CRH with an increase in plasma ACTH and cortisol production. The criterion for diagnosis of Cushing disease is a mean increase of 20% above baseline for cortisol values at 30 min and 45 min and an increase in the mean ACTH concentrations of at least 50% over the baseline value at 15 min and 30 min after CRH administration. 95% of patients with ACTH-independent Cushing syndrome show no response to CRH. Combined CRH/HDDST testing yields a diagnostic accuracy of 98%. The CRH test should be reserved for patients with confirmed Cushing syndrome since individuals with normal pituitary function respond to CRH like patients with Cushing disease.

Once the biochemical diagnosis has been made, *imaging studies* are useful to guide surgical therapy. Adrenal CT or MRI may visualize an adrenal tumor or macronodular or micronodular adrenal hyperplasia; ultrasound is inadequate. Pituitary MRI is the preferred method to localize the adenoma in Cushing disease. If no adenoma is seen (up to 50%), pituitary lateralization is performed in specialized centers with CRH and *inferior petrosal sinus sampling* (IPSS).

MANAGEMENT
Cushing Disease
Transsphenoidal surgery (TSS) is the treatment of choice for patients with Cushing disease. Success rate in specialized centers is variable (50–90%). Postoperative endocrine complications include diabetes insipidus (often transient), syndrome of inappropriate antidiuretic hormone secretion (SIADH), GH deficiency, central hypothyroidism, hypogonadism and pituitary apoplexy. Screening for GH deficiency may be necessary 3 months after TSS if linear growth does not improve. Permanent pituitary deficits are more common after repeat TSS and with larger adenomas. Pituitary irradiation is reserved for patients following a failed TSS; pituitary deficits are more common in this group. Newer forms of stereotactic radiotherapy are available; experience is limited in children.

Ectopic Adrenocorticotropic Hormone Syndrome
Cure of ectopic ACTH syndrome is possible only if the primary tumor is surgically curable (most typically bronchial/thymic carcinoid). If the primary tumor is not resectable, other means are used to correct the steroid excess state.

Adrenal Tumors
Surgical resection is the treatment of choice for benign adrenal tumors. Laparoscopic adrenalectomy (unilateral or bilateral) is widely available.

Adrenal Carcinoma
Therapy of adrenocortical carcinoma is less satisfactory because metastases are common at the time of diagnosis. Surgical excision

Child with increasing weight gain and suboptimal linear growth. Consider:
1. Hypothyroidism (obtain free T4, TSH)
2. Syndromes (Prader-Willi, pseudohypoparathyroidism)
3. Hypopituitarism (if headaches, obtain prolactin, IGF-1, LH, FSH, morning cortisol)
4. Cushing syndrome

#1–3 Ruled out

Perform screening tests for Cushing syndrome:
1. 24-hour UFC X 3
2. Overnight DST
3. Midnight cortisol levels (IV sample while asleep)

Normal

Abnormal, Cushing syndrome likely

Stop testing, no imaging needed. Follow for possible episodic Cushing syndrome

Additional testing to confirm the diagnosis and determine etiology

Testing to be considered:
1. ACTH levels to assess for ACTH dependence
2. Additional midnight cortisol testing (if needed)
3. LDDST, HDDST
4. Possible CRH test, IPSS to lateralize

LDDST normal, CS not confirmed

Result: LDDST abnormal, CS confirmed
Assess for ACTH dependence

ACTH dependent

ACTH independent

No suppression on HDDST

Suppression on HDDST

Diagnosis (adrenal source of CS):
1. ACT (adenoma or carcinoma)
2. PPNAD
3. Macronodular adrenal hyperplasia
4. McCune-Albright syndrome
Imaging: Adrenal CT or MRI, not US

CRH test: ACTH unchanged

CRH test: increased ACTH

Diagnosis : Ectopic ACTH syndrome
Imaging : Chest and abdominal CT or MRI
Octreotide scintigraphy may be helpful

Diagnosis : Cushing disease
Imaging : MRI of pituitary
If negative, CRH/IPSS study to lateralize before surgery

Figure 3 The diagnostic algorithm for Cushing syndrome in children. When faced with a child with increasing weight gain and suboptimal linear growth, the primary care physician will consider the differential diagnosis including hypothyroidism, pseudohypoparathyroidism, Prader-Willi syndrome and hypopituitarism. Appropriate screening tests for Cushing syndrome include 24-hour UFC, an overnight low dose DST and possibly an evening cortisol level to assess the circadian rhythm. If screening tests are suggestive of Cushing syndrome, additional testing will include more detailed dexamethasone suppression testing (LDDST, HDDST) to confirm the diagnosis. ACTH levels are included to assess for ACTH dependence. Low ACTH levels indicate ACTH independence and an adrenal lesion; adrenal imaging (MRI or CT) is then performed. In ACTH dependent cases, CRH testing may help distinguish Cushing disease from ectopic ACTH syndrome. IPSS is used in Cushing disease to aid in pituitary lateralization if the pituitary MRI is negative

Abbreviations: UFC, urine free cortisol; DST, dexamethasone suppression test; LDDST, low dose dexamethasone suppression test; HDDST, high dose dexamethasone suppression test; ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging; CT, computed tomography; CRH, corticotropin-releasing hormone; IPSS, inferior petrosal sinus sampling; T4, thyroxine; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; PPNAD, primary pigmented nodular adrenal disease; ACT, adrenocortical tumor; US, ultrasound; IGF-1, insulin-like growth factor; CS, Cushing syndrome.

is helpful to reduce the tumor mass and the degree of cortisol excess. Mitotane is the drug of choice for metastatic adrenal carcinoma. The dosage is 6–12 g/day orally in 3–4 divided doses. 70% of patients achieve a reduction of steroid secretion, 35% achieve a reduction in tumor burden.

Postoperative Management

- *Adrenal insufficiency.* In patients after successful TSS or unilateral adrenalectomy, HPA axis suppression is universal. Postoperatively, stress dose hydrocortisone (50 mg/m^2/day divided every 6-hour) should be given and gradually weaned to physiologic levels (6–10 mg/m^2/day divided TID) over many weeks to avoid adrenal crisis and symptoms of adrenal insufficiency. Stress-dose hydrocortisone is necessary for

months to a year or more with acute illness, trauma or surgical procedures until the HPA axis is determined to be normal.
- If the patient required bilateral adrenalectomy, lifelong glucocorticoid replacement is required with a gradual wean as described above postoperatively to physiologic dosing. Mineralocorticoid therapy (fludrocortisone, 0.05–0.2 mg PO daily) is also required. Episodic monitoring of the plasma renin activity and electrolytes is useful to adjust the fludrocortisone dose. Stress-dose hydrocortisone is needed for life.

OUTCOMES OR PROGNOSIS

Postoperative success is seen when the serum cortisol (or UFC) drops to an undetectable level. Patients are considered in remission if UFC is less than 10 µg/24 hours and morning plasma

cortisol values are low (< 1 μg/dL on postoperative day 3 or < 1.8 μg/dL at 8 am within 2 weeks). Recurrence risk in children with Cushing disease approximates 25% at 10 years. Untreated Cushing syndrome is eventually fatal. Death can relate to the tumor itself (ectopic ACTH syndrome, adrenal carcinoma) or can occur due to complications of hypercortisolemia including hypertension, cardiovascular disease, stroke, thromboembolism and infection. Individuals with a biochemical cure of Cushing disease have a life expectancy similar to age-matched controls, while patients with persistent hypercortisolism have an increased mortality rate. The prognosis in adrenal adenomas is excellent. In adrenal carcinoma, the prognosis is poor and the median survival from the date of onset of symptoms is about 4 years.

PREVENTION

Awareness of the signs and symptoms of Cushing syndrome facilitate early treatment. Healthcare providers should have a high index of suspicion for Cushing syndrome in the obese child with growth deceleration.

MORE ON THIS TOPIC

Bista B, Beck N. Cushing syndrome. Indian J Pediatr. 2014;81:158-64.

Kassi E, Chrousos G. The central CLOCK system and the stress axis in health and disease. Hormones (Athens). 2013;12:172-91.

Keil M, Stratakis C. Cushing syndrome in childhood. In: Radovick S, MacGillivray M. Pediatric Endocrinology: A Practical Clinical Guide. 2nd ed. New York: Springer; 2013. pp. 247-60.

Lila AR, Sarathi V, Jagtap V, et al. Cushing's syndrome: stepwise approach to diagnosis. Indian J Endocrinol Metab. 2011;15:S317-21.

Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med. 1994;331:629-36.

Miller W, Fluck C. Adrenal cortex and its disorders. In: Sperling M. Pediatric Endocrinology. 4th ed. Philadelphia, PA (USA): Elsevier; 2014. pp. 471-532.

Savage MO, Storr HL. Pediatric Cushing's disease: management issues. Indian J Endocrinol Metab. 2012;16:S171-5.

IN A NUTSHELL

1. Cushing syndrome is caused by chronic exposure to supraphysiologic doses of glucocorticoids.
2. Endogenous Cushing syndrome can be ACTH-independent (adrenal adenoma, adrenal carcinoma, hyperplasia, PPNAD) or ACTH-dependent (pituitary tumor or Cushing disease, ectopic ACTH syndrome).
3. Exogenous glucocorticoids such as prednisone, dexamethasone, and inhaled corticosteroids can cause a similar clinical phenotype. Children on these medications must be monitored carefully for evidence of Cushing syndrome.
4. Suspicion of Cushing syndrome should arise in the child with excessive weight gain and poor linear growth. Signs of adrenarche are common.
5. Loss of growth due to hypercortisolism is often permanent.
6. Proper biochemical confirmation and localization of Cushing syndrome is crucial before imaging to avoid unnecessary surgery.
7. Pituitary surgery for Cushing disease may lead to temporary or permanent hypopituitarism.

Chapter 44.18
Endocrine Hypertension
Praveen VP

Hypertension of endocrine etiology is distinctly rare in children and most of them are associated with endogenous hormone excess. Iatrogenic hormone excess can also result in hypertension. Among the hormones cortisol, aldosterone and other hormones of the adrenal steroidogenic pathway with mineralocorticoid activity as well as catecholamines, thyroid hormones and parathyroid hormone (PTH) are associated with hypertension. Hypertension associated with polycystic ovarian disease (PCOD) in the older adolescent and hypertension induced by steroid exposure also are included under the endocrine causes. Among these, the disorders related to various adrenal hormone excess are more common.

GENERAL APPROACH

There are no specific symptoms due to hypertension in children. When hypertension is detected in children, the etiology it is more likely vascular or renal or renovascular (see Chapter 41.18 on hypertension for details). Hence, it is prudent to rule out these causes first before investigating for an endocrine cause. There are a few exceptions to this, e.g., when there are symptoms like palpitations, sweating and anxiety which suggest catecholamine excess. Postural hypotension is frequently seen in pheochromocytoma due to the hypovolemia associated with the catecholamine excess. Hypokalemia in an older child is another pointer toward endocrine etiology although renal artery stenosis and Liddle syndrome need to be ruled out first. Strong family history of childhood onset hypertension and genital ambiguity increase the possibility of an endocrine cause for hypertension **(Flow chart 1).**

CATECHOLAMINES-RELATED HYPERTENSION

Hypertension due to catecholamine excess is usually seen in pheochromocytoma or paraganglioma and rarely in neuroblastoma or ganglioneuroma.

Pheochromocytoma and Paraganglioma

Although WHO classifies adrenal chromaffin tumors as pheochromocytoma and extra-adrenal chromaffin tumors as paraganglioma, for the purpose of this discussion both adrenal

Flow chart 1 Approach to diagnosis of endocrine hypertension
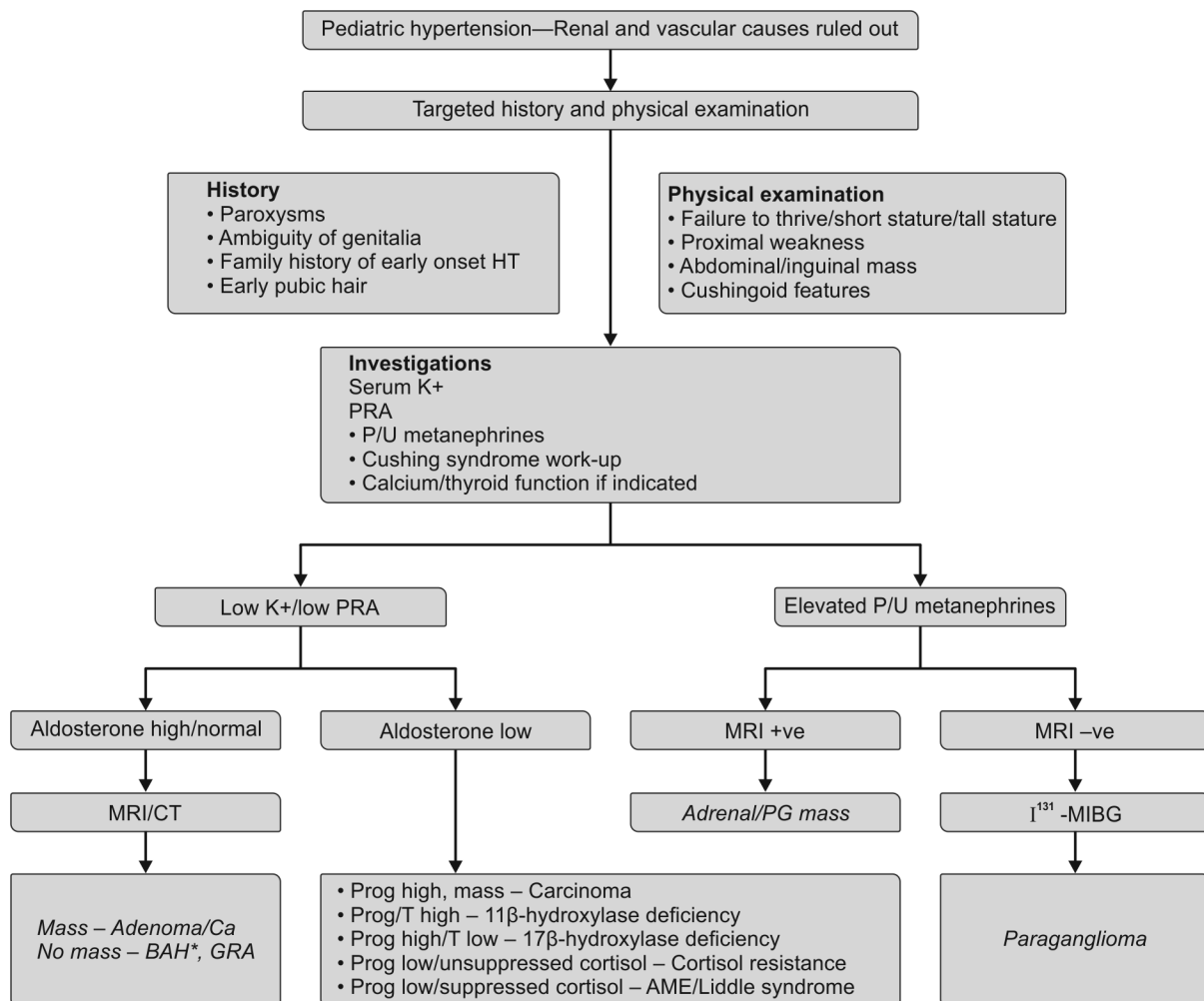
Abbreviations: AME, apparent mineralocorticoid excess; BAH, bilateral adrenal hyperplasia; GRA, glucocorticoid remediable hyperaldosteronism; HT, hypertension; T, testosterone; PRA, plasma renin activity; MRI, magnetic resonance imaging; CT, computed tomography; P/U, plasma or urine measurement; Prog, progesterone useful in prepubertal age group as the levels are virtually undetectable. Testosterone: any testosterone in the prepubertal age group more than 0.2 ng/mL is significant (due to assay sensitivity issues practically value needs to be repeated in borderline cases, especially if clinical suspicion is not strong).

* Rare variants of familial hyperaldosteronism are now described with bilateral nodularity.

pheochromocytomas and paragangliomas will be referred to as pheochromocytomas. Only 10–20% of pheochromocytomas occur in childhood. Peak age group is early in the second decade with a male predominance.

Certain clinical symptoms and signs if present are suggestive of pheochromocytoma. The classical triad of paroxysms seen in pheochromocytoma consists of palpitations, flushing attacks and anxiety. Persistent hypertension is more common than the classical paroxysms in childhood (70–80%). The blood pressure may range between 180 and 240 mm Hg systolic and 120–210 diastolic. The patient may be asymptomatic in between and during attacks may complain of headache, nausea, sweating, abdominal pain, dizziness and pallor. Features of hypertensive encephalopathy and seizures may also occur. It should be suspected if hypertension, hypotension, arrhythmias or symptoms suggestive of a crisis occur during an invasive procedure or after administration of drugs such as high dose steroids and metoclopramide. The other clinical features which are highly suggestive of pheochromocytoma include the presence of hypertension with mottling of skin or cyanosis, dilated or hypertrophic cardiomyopathy, new onset diabetes in the absence of Cushingoid features, pyrexia of unknown etiology or cerebral hemorrhage. Persistent unexplained hypotension and multiorgan dysfunction syndrome (MODS) with myoglobinuria and renal failure have been rarely described.

Most of the tumors secrete both epinephrine and norepi-nephrine with epinephrine predominating in adrenal tumors. Rarely, poorly differentiated tumors with dopamine production are observed. These frequently present with symptoms of local invasion or metastasis. Symptoms due to ectopic production of other hormones in a pheochromocytoma include persistent diarrhea due to vasoactive intestinal polypeptide (VIP), syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyperkalemia due to PTH-related peptide (PTHrP) and Cushing syndrome due to ectopic adrenocorticotropic hormone (ACTH) secretion.

More than 60% of the pheochromocytomas have a genetic basis. Many genetic syndromes such as neurofibromatosis type 1, von Hippel-Lindau syndrome and multiple endocrine neoplasia (MEN-2A, 2B) are known to have unilateral or bilateral adrenal involvement. Mutations in at least four genes increase the risk of developing the different types of hereditary paraganglioma-pheochromocytoma. Mutations in the *SDHD* gene predispose an individual to hereditary paraganglioma-pheochromocytoma type 1, mutations in the *SDHAF2* gene predispose to type 2, mutations in the *SDHC* gene predispose to type 3 and mutations in the *SDHB* gene predispose to type 4. These may be associated with tumors elsewhere in the body such as gastrointestinal stromal tumor (GIST), renal cell carcinoma and papillary thyroid carcinoma.

Neuroblastoma

It is rare for hypertension to be the presenting symptom of neuro-blastoma. As a rule, neuroblastomas are less efficient at processing catecholamines. Episodic sweating, flushing and hypertension can be present. Most of the metabolism of catecholamines is extratumoral. Monoamine oxidation in the liver and catechol O-methyltransferase (COMT) activity in the peripheral tissues convert the catecholamines to vanillylmandelic acid (VMA) or homovanillic acid (HVA).

DIAGNOSIS

Biochemical Testing for Pheochromocytoma

Diagnosis is established by the demonstration of elevated levels of catecholamines and/or their metabolites in a 24-hour specimen of urine. The predominant catecholamine in children is

norepinephrine, and total urinary catecholamine excretion usually exceeds 300 μg/24 hours.

Pheochromocytomas are very efficient at synthesizing, storing and metabolizing catecholamines. Intratumoral metabolism of catecholamines to metanephrine via COMT pathway continues even when the secretion into the circulation is absent. The enzymes of the monoamine oxidase (MAO) pathway, which lead to the synthesis of VMA, are present in peripheral tissues including the liver. Estimation of VMA may be normal when the tumor is not actively secreting. Endogenous and exogenous factors, especially drugs can fallaciously lead to higher catecholamine levels and consequently higher catecholamine metabolite levels.

24-hour urine collection is essential for urine metabolite estimation. Age specific cut-offs are used in interpretation, which vary from lab to lab. Timed collections corrected for urine creatinine are possible but inferior to 24-hour collection. Most of the urine assays for VMA and metanephrine need acidified urine and hence 10–20 mL in hydrochloric acid needs to be added to the collection container prior to collection to ensure stability to maintain a pH of less than or equal to 3. Many assays for VMA require refrigeration (4–8°) of the urine during the collection process itself. Adequacy of collection needs to be verified by estimating 24-hour urine creatinine.

Estimation of catecholamines and fractioned free meta-nephrines in plasma obviates the need for cumbersome 24-hour urine collections in children. Strict guidelines need to be followed in the process which includes sampling via a venous catheter which has been placed for at least 20 min. This is to offset the false positivity resulting from the stress associated with venous catheter placement. Fasting sample is preferred and most assays procedures would also recommend transportation of these samples to the lab at 4–8°C.

In pheochromocytoma, estimation of plasma free and urine fractionated metanephrines by high performance liquid chromatography (HPLC) followed by electrodetection or by tandem mass spectrometry estimation has emerged as the investigation with the highest sensitivity and specificity. It would seem that screening in cases of low levels of suspicion is best done by plasma metanephrines.

Imaging

Anatomical Imaging

MRI is preferred. Pheochromocytoma typically is T2 hyperintense. Most tumors are more than 3 cm in size at diagnosis. CT scan can be used in the older child.

Functional Imaging

This is indicated in extra-adrenal paraganglioma to rule out multifocal tumors, adrenal pheochromocytomas of more than 10 cm in size to rule out metastasis, and in tumors where bio-chemical tests are positive with anatomical imaging negative. Iodine[131]-metaiodobenzylguanidine (I[131]MIBG) is the first line functional imaging modality. Recently, positron emission tomography-computerized tomography (PET-CT) scans with flourodeoxyglucose (FDG), F-dihydroxyphenylalanine (DOPA) and F-dopamine (DA) have become available, which have a higher sensitivity.

MANAGEMENT

Surgical treatment is the mainstay of management if the tumor is resectable. Preoperative preparation with alpha-blocker preferably noncompetitive followed by beta-blockers for at least 1 week is recommended prior to surgery. A brief outline of the preoperative management is given in **Table 1**. Laparoscopic surgery is preferred for tumors less than 8 cm size. In patients with bilateral tumors,

Table 1 Preoperative management of pheochromocytoma

Principles	Drugs used	Postoperative
• Institute alpha-blockade first, preferably by noncompetitive agents • Beta-blockers to control tachycardia are added once alpha-blockade is achieved (stuffy nose is an indicator) • Volume expansion and correction of anemia is done before surgery by blood transfusions, salt rich diet and saline infusion • Preoperative blood pressure control with nitroprusside • Volume expansion during surgery is important to prevent postoperative hypotension	• Phenoxybenzamine (nonselective noncompetitive alpha-blocker) 0.5–1 mg/kg/12 hours • Phentolamine (nonselective competitive IV) 1 mg 1–2 hours before surgery and during surgery • Prazosin 1 mg TID up to 20 mg • Doxazosin 1 mg TID up to 12 mg • Atenolol 1–2 mg/kg/day • Nifedipine • Sodium nitroprusside 0.5–5 µg/kg/min • Metyrosine (competitive tyrosine hydroxylase inhibitor) 250 mg BID to TID	• Postoperative hypotension is common due to catecholamine withdrawal • Patients may go into hypoglycemia due to sudden loss of suppressive effects of catecholamines on the β-cells

cortical-sparing surgery which preserves the adrenocortical function is preferred. PASS (Pheochromocytoma of the adrenal gland scaled score) score is used to assess the malignant potential when there are no detectable metastases. Patients are followed-up with plasma or urine metabolite estimation at yearly interval for at least 5 years for sporadic tumors and life-long for cases with germline mutation or familial etiology. Chromogranin A is another marker which is useful for follow-up. Metastatic tumors are treated with I[131]MIBG therapy. The role of chemotherapeutic regimens in children is less clear.

MINERALOCORTICOID RELATED HYPERTENSION (LOW RENIN HYPERTENSION)

Aldosterone-Related Causes
Hypertension related to aldosterone hypersecretion is rare in pediatric population. Both congenital and acquired forms are possible and are indicated in the **Table 2**. All the causes are characterized by suppression of renin levels. Hypokalemia is usually a late development and may not always be present at the time of diagnosis.

Other Hormones with Mineralocorticoid Action
11-deoxycortisol and 11-deoxycorticosterone are two intermediates of the steroidogenic pathway which have mineralocorticoid activity and are associated with clinical states resulting in hypertension. These conditions are summarized in the **Table 3**.

DISORDERS OF CORTISOL PRODUCTION OR METABOLISM

These are detailed in **Table 4**.

Basic Principles in Biochemical Testing
1. Most renin assays measure rate of angiotensin I generation which is expressed as plasma renin activity in ng/mL/hour. Direct renin assays have become available in the last decade.
2. Renin values are age specific. As a general rule, neonates have high values in double digits which decrease to single digit figures by the end of 1 year.
3. Aldosterone or renin ratios have not been validated in children, but probably can be used in older adolescents.

OTHER CAUSES
- *Thyroid diseases* Both hyperthyroidism and hypothyroidism are associated with hypertension. The thyroid problem is often obvious or hypertension is detected as an incidental finding.
- *Hyperparathyroidism* Primary hyperparathyroidism as such is rare in pediatric population except when it is associated with genetic syndromes like MEN-1 or hyperparathyroidism-jaw tumor syndrome. Mild hypertension is often noted which disappears with successful treatment of the primary condition.

Table 2 Aldosterone-related hypertension

Conditions	Mechanism	Diagnostic biochemical abnormalities	Comments
Adrenal adenoma/BAH	Hypersecretion of aldosterone by tumor or hyperplastic tissue	• Suppressed renin • Normal/high aldosterone for age • High aldosterone/renin ratio	• Hypokalemia frequent • Surgery for adenomas • Medical treatment for bilateral hyperplasia • BAH is more common in children
Adrenal carcinoma	Hypersecretion of aldosterone by tumor	As above	Usually associated with other hormone excess, large mass
GRH	Aldosterone synthesis takes place in zona fasciculata under control of ACTH due to a cross-over and fusion of the promoter of ACTH responsive part of the 11β-hydroxylase 1 gene to the coding region of the aldosterone synthase gene	As above	• Strong family history of early onset refractory hypertension and stroke • Hypokalemia may not be present • Treatment with glucocorticoids

Abbreviations: GRH, glucocorticoid-remediable hyperaldosteronism; BAH, bilateral adrenal hyperplasia; ACTH, adrenocorticotropic hormone.

Table 3 Hypertension due to intermediates of steroidogenic pathway

Clinical condition	Mechanism	Clinical presentation	Diagnosis#	Treatment and comments
11β-hydroxylase deficiency	• Conversion of deoxycortisol to cortisol and deoxycorticosterone to corticosterone decreased resulting in their accumulation • Diversion of the steroid synthetic pathway to the androgen pathway	• Virilized female neonate • Postnatal virilization and accelerated growth if untreated in both genders	• Suppressed renin • Elevated DOCA and deoxycortisol	Hydrocortisone at a dose of 12–18 mg/m^2
17α-hydroxylase deficiency	Accumulation of DOCA#	Early presentation: • Undervirilized male (mild to extreme) and normal female at birth. • Extreme undervirilization of male with female like external genitalia with palpable gonads possible Late presentation: Delayed puberty in an apparent female	• Suppressed renin • Elevated DOCA	As above

Abbreviation: DOCA, deoxycorticosterone acetate.
 # Elevation of progesterone levels is a cost effective investigation which along with suppressed renin gives valuable clue to the diagnosis.

Table 4 Disorders of cortisol production or metabolism

Condition	Mechanism	Presentation	Comments
Cushing syndrome	High levels of cortisol exert mineralocorticoid action	Refer to Chapter 44.17	Refer to Chapter 44.17
Cortisol resistance syndrome	Decreased cortisol action, due to defect at the level of glucocorticoid alpha-receptor or steroid receptor complex, resulting in poor ACTH feedback suppression, high ACTH levels and consequent higher levels of DOCA, cortisol and androgens. Excess cortisol acts via mineralocorticoid receptor	Hypokalemic alkalosis Hirsutism and acne XX virilized female described in severe homozygous defect	Heterozygous mutations are more described than the homozygous defect Heterozygous defect results in only partial cortisol resistance
Apparent mineralocorticoid excess	11β-hydroxysteroid dehydrogenase type 2 converts cortisol to cortisone at the level of kidneys and prevents cortisol action at the level of mineralocorticoid receptor—inactivating mutation allows cortisol to act on the receptor	Failure to thrive with hypertension and hypokalemic alkalosis	Altered ratio of cortisol to cortisone metabolites in the urine

Abbreviations: ACTH, adrenocorticotropic hormone; DOCA, deoxycorticosterone acetate.

IN A NUTSHELL

1. Endocrine hypertension is often related to disorders involving the adrenal glands—disorders of the adrenal cortex with excess production of mineralocorticoids or glucocorticoids which may have a congenital or acquired basis.
2. Pheochromocytoma, a catecholamine-secreting tumor, arising from the chromaffin cells of the adrenal medulla manifests with paroxysmal or persistent hypertension in children.
3. Diagnosis is established by the demonstration of elevated levels of catecholamines and/or their metabolites in a 24-hour specimen of urine.
4. Surgery for pheochromocytoma requires with appropriate preoperative management.
5. Hypertension in children may be due to excess cortisol or disorders of cortisol production.

MORE ON THIS TOPIC

DeLellis RA, Lloyd RV, Heitz PU. Pathology and Genetics of Tumours of Endocrine Organs. Lyon: IARC Press; 2004.

Ingelfinger JR. Hypertension in children: endocrine considerations. In: Lifshitz F. Textbook of Pediatric Endocrinology. 5th ed. New York: Informa Healthcare; 2007. pp. 261-78.

Lowery AJ, Walsh S, McDermott EW, Prichard RS. Molecular and therapeutic advances in the diagnosis and management of malignant pheochromocytomas and paragangliomas. Oncologist. 2013;18:391-407.

Parsa AA, New MI. Low-renin hypertension of childhood. Endocrinol Metab Clin North Am. 2011;40:369-77.

Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2010;95:2023-37.

Whiting MJ, Doogue MP. Advances in biochemical screening for phaeochromocytoma using biogenic amines. Clin Biochem Rev. 2009;30: 3-17.

Chapter 44.19
Glucocorticoid Use and Withdrawal
VK Bhardwaj

Glucocorticoid is the term used for pharmaceuticals which predominantly have anti-inflammatory, immunomodulatory and metabolic activity with variable degree of effect on electrolyte metabolism. Cortisol is the natural glucocorticoid secreted by the adrenal cortex. Endogenous secretion of cortisol by the adrenal gland is under negative feedback control of the hypothalamus and pituitary glands. This feedback loop is referred to as hypothalamic-pituitary-adrenal axis (HPA axis) which fine tunes adrenal secretion to ensure availability of the hormone as per the requirement of the body at a given point of time.

PHARMACEUTICAL PREPARATIONS OF GLUCOCORTICOIDS

Pharmaceutical preparations of glucocorticoids are available as an injection (for intramuscular, intravenous or intra-articular use), as tablet, syrup and drop (for oral use), as spray (for nasal use), as dry powder and metered-dose inhaler (for respiratory use) and as ointment, gel, cream and lotion (for topical use). These are used in clinical practice for therapeutic purpose and diagnostic purpose (e.g., overnight dexamethasone suppression test and low dose dexamethasone suppression test for assessment of endogenous hypercortisolemia).

Diagnostic use and therapeutic use of low doses of inhaled preparations and topical preparation usually do not lead to systemic side effects. High dose inhalational preparations and long use of topical preparation over a large area can at times have systemic effect, mainly in the form of HPA axis suppression, adverse effect on physical growth and disturbance of ovarian function in a girl.

Parenteral preparations of glucocorticoids are usually used for short duration or intermittently and commonly do not lead to systemic side effects when used for 5 days or less. However, longer than 5 days use and/or frequent courses of short duration may lead to systemic toxicity and/or HPA axis suppression requiring attention.

Relative biologic potencies of synthetic steroids are compared in **Table 1**.

Table 1 Relative biologic potencies of synthetic steroids in bioassay systems

Steroid	Anti-inflammatory action	HPA axis suppression	Salt retention
Cortisol	1	1	1
Prednisolone	4	4	0.75
Methylprednisolone	6.2	4	0.5
Fludrocortisone	12	12	125
Triamcinolone	5	4	0
Dexamethasone	26	17	0

Source: Adapted from Stewart PM. The Adrenal cortex. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology. 11th ed. Noida: Saunders, Elsevier; 2009. pp. 445-503.

ADVERSE EFFECTS OF GLUCOCORTICOID THERAPY

In usual clinical practice, it is the oral glucocorticoid preparations which are used, misused and/or abused for long periods and cause systemic toxicity and HPA axis suppression. The adverse effects depend on the dose and potency of the preparation and the duration for which it is administered. In general, a dose of greater than 5 mg/m^2 body surface area per day of oral prednisolone (or equivalent dose of other glucocorticoid preparation) is liable to cause adverse effects when used for longer than 21 days at a stretch. HPA axis suppression usually does not occur with use below 2 weeks, and the steroid can be stopped abruptly. For use above 4 weeks, it should be presumed to have caused suppression, necessitating a slow taper. However, shorter courses used repeatedly can lead to clinically significant adverse effects and suppression of HPA axis.

The adverse effects are the extension of pharmacological effects. These preparations increase appetite and consequent increase in food intake leads to weight gain which predominantly is in the form of fat accumulation in a centripetal manner. There is round face, development of double chin, buffalo hump and abdominal obesity **(Fig. 1)**. Limbs are not fattened and in fact in late stages and in severe toxicity they become thin. The catabolic effect of the drug may lead to muscle wasting and weakness. Skin becomes thin and stretched leading to development of red or blue stretch marks over trunk, limbs and shoulders **(Fig. 2)**. There may be subcutaneous bleed after trivial trauma. Blood pressure may

Figure 1 Moon facies of a 4-month-old girl (misuse of betnesol drops)

Figure 2 Typical red, depressed striae of Cushing syndrome. The patient was on prolonged prednisolone for reactive airway disease

rise. There may be rise in plasma glucose once the glucocorticoid-induced insulin resistance becomes so severe that it can no longer be compensated by increased insulin secretion by the pancreas. Immune suppression predisposes the recipient to contract bacterial, viral and/or fungal infections. Anti-inflammatory effect of glucocorticoid impairs the body's response to infection and thus the infection may not be detected early due to paucity of symptoms. Suppression of growth hormone (GH) effect can cause physical growth failure. Interference with gonadal function can lead to menstrual irregularity in girls. Increase in osteoclastic activity and suppression of osteoblastic function can cause osteopenia or osteoporosis. Suppression of HPA axis renders the recipients unable to produce cortisol endogenously, thereby making them dependent on exogenous supply. The HPA axis reactivation may take weeks for achieving normal functional status. The recipient may need exogenous dose during stressful situations even several weeks after the withdrawal of the drug.

GLUCOCORTICOID WITHDRAWAL

In patients on therapeutic dose of glucocorticoid preparation, the timing and rate of withdrawal is determined by the response of the primary disease for which it is used. Too quick a withdrawal may lead to a flare-up of the primary disease. Sometimes, the development of severe systemic toxicity or intercurrent infection in the recipient may necessitate earlier withdrawal of the drug.

When the drug is withdrawn due to toxicity or in a case of drug misuse or abuse, the dose is halved every 7–14 days till the physiological replacement dose of 10 mg/m^2 daily of hydrocortisone or almost 2.5 mg/m^2 body surface area per day of prednisolone (or equivalent of other glucocorticoid) is achieved. At this point, the total daily dose is given once a day early morning on waking for 14 days and thereafter reduced by 0.5 mg/m^2 every 10–14 days till a daily dose of almost 2 mg/m^2 body surface area per day of prednisolone equivalent is achieved. At this point, the dose is administered on alternate days for another 14 days. If the patient is clinically stable, has normal appetite and vitals, the drug can be stopped. However, the HPA axis may still be suppressed and the patients are counseled to take glucocorticoid in stress doses (5–15 mg/m^2 per day prednisolone equivalents) during illness and consult the doctor. The activity of the HPA axis can be assessed by measuring plasma adrenocorticotrophic hormone (ACTH) and serum cortisol at 8 am. Adrenal cortical responsiveness can also be assessed by measuring serum cortisol, 1 hour after IM or IV administration of cosyntropin or synacthen (a synthetic derivative

of ACTH). Normal response would be serum cortisol concentration greater than 20 μg/dL after cosyntropin. Insulin tolerance test (ITT) can also be performed to assess the responsiveness of HPA axis. Any measurement of serum cortisol must be done after stopping prednisolone for 48 hours (or substituting with an equivalent dose of dexamethasone), as prednisolone cross-reacts significantly in the cortisol assay. Chapter 44.16 also deals with testing for glucocorticoid insufficiency.

IN A NUTSHELL

1. The adverse effects of glucocorticoids depend on the dose and potency of the preparation and the duration for which it is administered.
2. Oral prednisolone in a dose more than 5 mg/m^2 body surface area per day is liable to cause adverse effects when used for longer than 21 days at a stretch.
3. The adverse effects are the extension of pharmacological effects.
4. High dose inhalational preparations and long use of topical preparation over a large area can at times have systemic effect, mainly in the form of HPA axis suppression, adverse effect on physical growth and disturbance of ovarian function in a girl.
5. Parenteral preparations of glucocorticoids when used for more than 5 days and used in frequent courses of short duration may lead to systemic toxicity and/or HPA axis suppression.
6. The timing and rate of withdrawal of steroids is determined by the response of the primary disease for which it is used.
7. The activity of HPA axis can be assessed by measuring plasma ACTH and serum cortisol at 8 am.

MORE ON THIS TOPIC

Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of complications of systemic steroid therapy. Allergy Asthma and Clin Immunol. 2013;9:30.

Raghupathy P. Approach to adrenal insufficiency. In: Shah NS, Rao S. IAP Specialty Series on Pediatric Endocrinology. 2nd ed. Gwalior: IAP National Publication House; 2013. pp.163-9.

Stewart PM. The Adrenal cortex. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology. 11th ed. Noida: Saunders, Elsevier; 2009. pp. 445-503.

Chapter 44.20
Disorders of Sexual Development

Ganesh S Jevalikar, Preeti Dabadghao

The birth of a child with ambiguous genitalia is a stressful situation for the family, since "*is it a boy or a girl?*" is usually the first question asked. Problems related to genital development, unlike many other malformations, often lead to stigmatization of the child and family and hence need to be handled with great care and sensitivity. In addition, life-threatening emergencies may be averted with timely diagnosis. This chapter deals with basics of gender development, differentiation, clinical presentation and issues in diagnosis and management of a child with disorders of sexual development (DSD). A plethora of genes, signaling mechanisms and transcription factors are involved in each step of sex development and differentiation; however, a detailed discussion of genetic and molecular mechanisms is beyond the scope of this chapter.

TERMINOLOGIES AND DEFINITIONS

Typically, a 46,XY karyotype leads to development of testes and male genitalia and 46,XX to ovary and female genitalia. DSD include a heterogeneous group of conditions where there is lack of consonance between chromosomal, gonadal and phenotypic sex. The term DSD has now replaced the previously used terminology *intersex*, perceived as potentially pejorative. A consensus statement published in 2006 introduced several new terminologies **(Table 1)** to replace older diagnostic labels. The term DSD also encompasses conditions which may not present with genital ambiguity (Klinefelter syndrome, Turner syndrome) and atypical conditions like cloacal exstrophy. Some definitions commonly used in DSD cases are summarized in **Table 2**.

Table 1 Revised nomenclature of DSD (proposed in 2006)

Previous terms	New nomenclature
Intersex	DSD
Male pseudohermaphrodite	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Abbreviation: DSD, disorders of sexual development.

DEVELOPMENT OF THE REPRODUCTIVE SYSTEM

The primitive gonad is formed as a condensation of intermediate mesoderm on either side of the developing aorta in the region of the mesonephros (urogenital ridge). Germ cells migrate in this area under the influence of signaling molecules and proliferation of coelomic epithelium gives rise to sex cords. Wolffian (mesonephric) and Müllerian (paramesonephric) ducts **(Fig. 1)** develop on the side of each gonad and extend caudally. The primitive gonad is bipotential (i.e., it can develop into an ovary or testis) till 6 weeks of gestation.

It has long been thought that the development of testis from undifferentiated gonad is an active process driven by key genes and absence of these leads to ovarian differentiation in a passive manner. However, emerging evidence indicates that ovarian development is also an active process. The presence of a Y chromosome and expression of the sex determining region on Y chromosome (*SRY*) gene in the gonad determines testes development. *SRY* activation with synergistic SF1 (steroidogenic factor 1) expression leads to increased expression of *SOX9* (*SRY box 9*) which promotes testicular differentiation and suppresses antitestes factors (DAX1, RSPO1, WNT-4) **(Flow chart 1)**.

Important genes determining ovarian development include *WNT-4* (wingless type MMTV integration site family, member 4), *RSPO1* (R-spondin1) and *FOXL2* (forkhead transcription factor).

HORMONES IMPORTANT IN SEX DEVELOPMENT

Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) is a glycoprotein hormone. In early fetal life, testes (sertoli cells) are the only source of AMH which through its receptor AMHR2 is responsible for regression of Müllerian structures in male fetuses. Lack of AMH in a genetic male fetus due to gonadal dysgenesis or mutations in AMH or AMHR2 leads to persistence of the uterus. In the latter case, external genitalia are normal since Leydig cell function is not affected.

Testosterone and Dihydrotestosterone

Testosterone and dihydrotestosterone (DHT) are secreted by the fetal Leydig cells by 8–9 weeks postconception and a marked increase in their levels is seen by 16 weeks of gestation. Leydig cell steroidogenesis is controlled by human chorionic gonadotropin (hCG) in the first two trimesters and by fetal luteinizing hormone (LH) in the last trimester of pregnancy. DHT is produced from testosterone by peripheral conversion by 5α-reductase enzyme. It causes enlargement of the phallus, fusion of labioscrotal folds to form scrotum and fusion of the urethral folds from posterior to anterior direction to form a penile urethra. AMH and testosterone act on the ipsilateral side of production to cause Müllerian regression and Wolffian stabilization respectively. Descent of

Table 2 Various terminologies used in cases of DSD

Terminology	Definition/explanation
Chromosomal sex	Complement of sex chromosomes present in an individual (46,XX; 46,XY)
Gonadal sex	Development of gonadal tissue as testis or ovary
Phenotypic (anatomic) sex	Presence of male or female external and internal genitalia
Mosaicism	Presence of two different cell lines arising from a single zygote (usually a result of mitotic nondisjunction)
Chimerism	Two or more cell lines with different genetic origin in an individual (usually result of double fertilization of binucleate ovum, fusion of two zygotes or fertilization of ovum and its polar body by separate sperms)
Gender identity	Person's self identification as male or female
Gender role	Expression of characteristics that are sexually dimorphic within a general population (clothing/toys preferences, physical aggression, grooming behavior, etc.)
Sexual orientation	Choice of sexual partner and erotic interest (heterosexual, homosexual, bisexual)

Figure 1 Development of internal genitalia

the testes into the scrotum is a combination of mechanical and hormonal factors influenced by genes like *INSL3* and *CGRP* in addition to genes involved in hormone synthesis. Actions of these hormones and derivatives of primitive genital structures in male and female are summarized in **Flow chart 1** and **Table 3** respectively.

Steroidogenic Pathways

Steroid biosynthesis takes place from cholesterol in the steroidogenic organs (principally adrenals, gonads and placenta). **Flow chart 2** outlines the classical pathway of steroidogenesis. A block in any step leads to increased precursor which may be diverted to unaffected pathways. It also leads to feedback activation of controlling hormone [like adrenocorticotropic hormone (ACTH) in cortisol deficiency]. An alternative pathway of synthesis of DHT from 17-hydroxyprogesterone (17OHP) and progesterone has been described in tammar wallabies and is likely to play a significant role even in humans as evidenced from studies on patients with 21-hydroxylase deficiency and the newly described P450 oxidoreductase (POR) deficiency.

DISORDERS OF SEX DEVELOPMENT

Box 1 lists currently used nomenclature and examples of conditions causing DSD. Classic 21-hydroxylase deficiency is the most common cause of genital ambiguity. This and some other common and important conditions are discussed below.

46,XX DSD

Exposure to androgens at the critical time of external genital development leads to virilization of female external genitalia. The most common cause of 46,XX DSD is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (90–95% cases of CAH), other causes being listed in **Table 4**.

Congenital Adrenal Hyperplasia

Enzyme 21-hydroxylase (*CYP21A2*) converts progesterone and 17OHP to deoxycorticosterone and deoxycortisol respectively. Deficiency therefore leads to impaired production of mineralo-corticoids and glucocorticoids **(Flow chart 2)**, causing increased secretion of ACTH by normal feedback mechanisms. The elevated

Flow chart 1 Development of the reproductive system
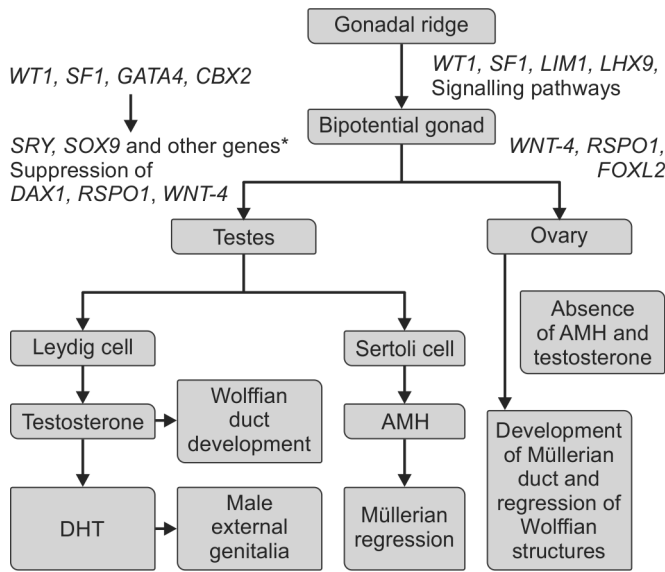
Abbreviations: WT1, Wilms tumor 1; SF1, steroidogenic factor 1; LIM1, Lim homeodomain transcription factor 1; LHX9, LIM homeobox 9; GATA4, GATA binding protein 4; CBX2, chromobox homolog 2; SRY, sex determining region on Y; SOX9, SRY box 9; DAX1, Dosage-sensitive sex reversal, adrenal hypoplasia, critical region on chromosome X, gene 1; RSPO1, R-spondin1; WNT-4, wingless type MMTV integration site family, member 4; FOXL2, forkhead transcription factor; AMH, anti-Müllerian hormone; DHT, dihydrotestosterone

*other genes include *DHH* (desert hedgehog); *DMRT1* (doublesex, mab-3 related transcription factor 1); *ARX* (aristaless-related homeobox, X-linked) and *ATRX* (alpha thalassemia mental retardation, X-linked).

ACTH produces adrenal hyperplasia and also drives the formation of excessive amounts of precursors including 17OHP which is then diverted to androgen production. This results in genital ambiguity in females. Boys do not have ambiguity (since excess androgen will not affect male external genitalia in utero), hence are at risk of missed diagnosis, adrenal crisis and death.

The gene coding for 21-hydroxylase (*CYP21A2*) is situated on chromosome 6p21.1 in the human leukocyte antigen (HLA) region and mutations are a result of gene conversions, in which part or whole of the gene is replaced by structurally homologous pseudogene *CYP21A1*. The severity of the mutation influences the expression of enzyme activity with the classic form (either salt wasting or simple virilizing) resulting from less than 5% of the enzyme activity. The simple virilizing form (20–25%) presents with androgen excess without clinical features of salt wasting. Boys and unrecognized girls may present later with peripheral precocious puberty. The nonclassic form presents with premature adrenarche or symptoms of hyperandrogenism at puberty but not with genital ambiguity.

The diagnosis can be made by newborn screening done on a filter paper sample taken after 72 hours of life or on a peripheral venous sample. The diagnosis depends on severe elevations of 17OHP (usually > 100 ng/mL). The management of 21-hydroxylase deficiency is discussed briefly in **Box 2** and in detail in Chapter 44.15.

Other Causes of 46,XX DSD
Table 4 describes other forms of CAH and other conditions presenting with 46,XX DSD. In addition, maternal virilizing tumors or androgen intake can also be underlying causes. A small proportion of patients may have 46,XX testicular DSD (due to the expression of *SRY* or other genes promoting testicular differentiation on the X chromosome), which can present with ambiguity or normal male genitalia with hypergonadotropic hypogonadism.

46,XY DSD
Disorders of Gonad Development
46,XY gonadal dysgenesis refers to failure of formation of the gonad in the presence of nonmosaic male karyotype. It can be further classified into complete (no differentiation, also termed Swyer syndrome or 46,XY pure gonadal dysgenesis) and partial (some evidence of differentiation). In complete dysgenesis, absence of AMH or androgens leads to completely female external genitalia with persistence of Müllerian structures. Detectable or normal testosterone due to excess LH action on theca cells in some cases leads to clitoromegaly. Since there is no ambiguity, many cases may present with delayed puberty or primary amenorrhea or infertility (as there is no functioning ovarian tissue). Wolffian structures are absent. Gonadal malignancy risk is high in these cases. Gonadectomy and cyclical hormonal therapy are required. Presence of a uterus allows in vitro fertilization and pregnancy.

Partial gonadal dysgenesis can manifest with mild or severe genital ambiguity. The extent of functioning testicular tissue determines development or absence of Müllerian or Wolffian structures. Gonads are usually intra-abdominal or inguinal but may be scrotal rarely. Skeletal features of Turner syndrome may be present in about 15–20% cases. Levels of testosterone are typically low at baseline and following hCG stimulation. Risk of gonadal tumors is 15–30%. Although several genes have been identified to be associated with gonadal dysgenesis **(Table 5)**, a molecular cause can be identified only in 20% of the cases.

Disorders of Androgen Biosynthesis
Box 1 lists the disorders of androgen biosynthesis. Steps which affect both adrenal and gonadal steroidogenesis [StAR, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17-hydroxylase/17,20-lyase, POR] present with a combination of adrenal and gonadal defects. As a group, the following points are important in androgen biosynthesis disorders:

Table 3 Derivatives of primitive genital structures in males and females

Primitive structures	Male	Female
Bipotential gonad	Testes	Ovary
Wolffian duct	Rete testes, epididymis, vas deferens, seminal vesicles	Regresses
Müllerian duct	Regresses	Fallopian tube, uterus, cervix, upper two-thirds of vagina
Phallus	Penis	Clitoris
Labioscrotal folds	Scrotum	Labia majora
Urethral folds	Penile urethra	Labia minora
Urogenital sinus opening	Urethral opening (common to urinary and genital tract)	Separate urethral and vaginal openings

Flow chart 2 Steroidogenesis pathways
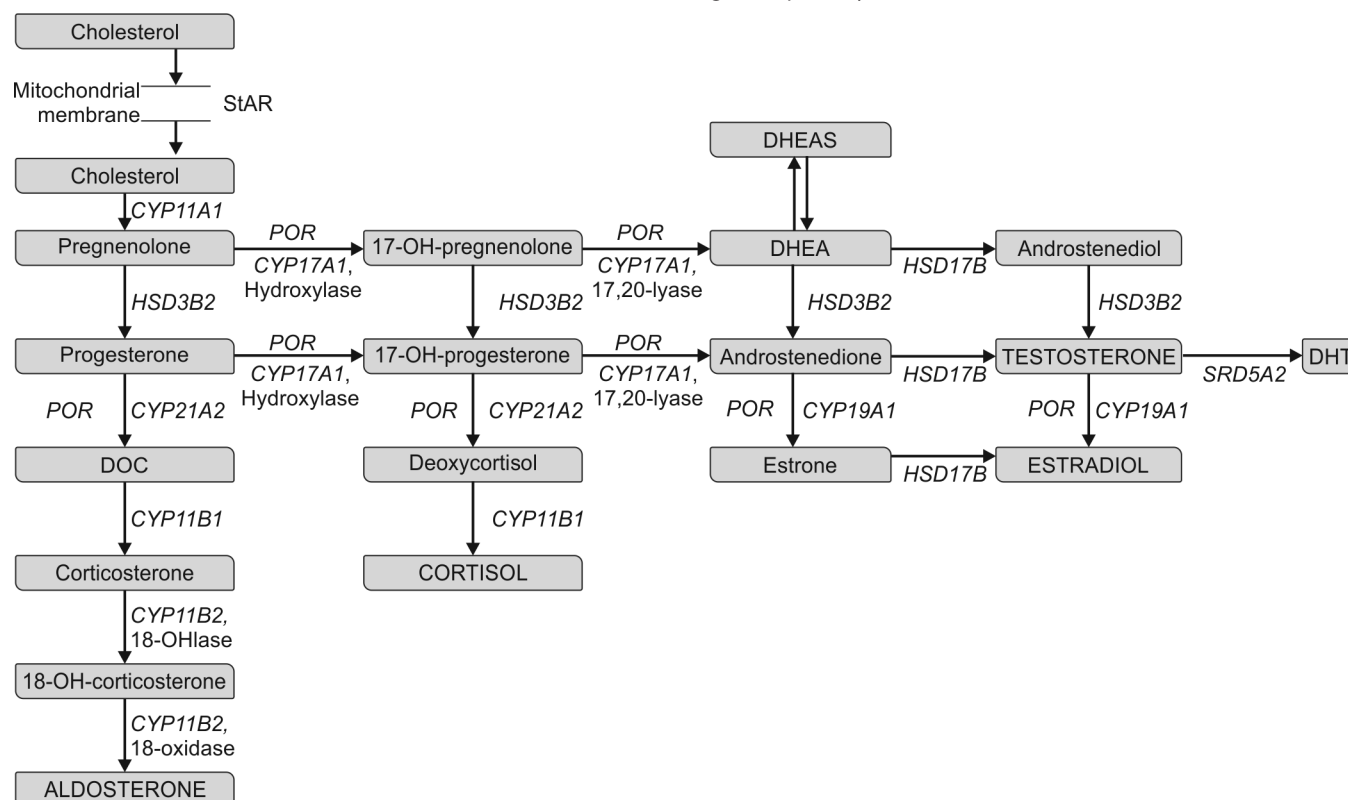
Abbreviations: StAR, steroidogenic acute regulatory protein; DOC, deoxycorticosterone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone. Alternative enzyme names: CYP11A1, P450 side-chain cleavage or 20,22-desmolase; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYP21A2, 21-hydroxylase; CYP11B1, 11β-hydroxylase; CYP11B2, it has three actions: (i) 11β-hydroxylase, (ii) 18-hydroxylase and (iii) 18-oxidase; POR, P450 oxidoreductase; CYP19A1, aromatase; HSD17B, 17β-hydroxysteroid dehydrogenase; SRD5A2, 5α-reductase type 2.

- The gonads are differentiated testes and their location may be intra-abdominal, inguinal or scrotal.
- Müllerian structures are absent since AMH production is normal.
- Appearance of external and internal genitalia is usually symmetric. Variable features may be seen depending on severity of defect ranging from hypospadias, micropenis, cryptorchidism. A blind vaginal pouch may be present.
- Wolffian structures are present, although they may be hypoplastic in some conditions (LH receptor defect, 3β-HSD) or well differentiated in others (5α-reductase, 17β-HSD 3 deficiency). Elevated LH levels are seen in infancy and from pubertal age.

Some of the important clinical and biochemical features of these disorders are summarized in **Table 6**. Features of 3β-HSD and POR deficiency which can cause ambiguity in both sexes are described in **Table 4**.

Other XY DSD

Vanishing testes syndrome, in which in utero vascular accident causes regression of testes in the embryonic period, can present with genital ambiguity. Insult in later gestation present with normal external genitalia.

Persistent Müllerian duct syndrome results from mutations in the AMH gene or AMH receptor and presents with normal male external genitalia with the presence of a uterus. An incidental diagnosis may be made during hernia repair. Testes may be undescended and the vas may be embedded in close proximity to the uterus.

Sex Chromosome DSD

Klinefelter and Turner syndromes and their variants are common chromosomal aneuploidies (1 in 500 and 1 in 2,000 conceptuses respectively) having characteristic clinical features discussed elsewhere in this book.

45,X/46,XY Mosaicism
(Mixed Gonadal Dysgenesis)

Mosaicism results from mitotic nondisjunction in a zygote. External genital phenotype varies from near normal female genitalia to a variable degree of ambiguity to near normal penis. The gonads may be a combination of fibrous streaks or dysgenetic testes with or without one normal testis located anywhere along the path of testicular descent. Histology may be different between two gonads as well as within a single gonad giving rise to the term mixed gonadal dysgenesis. Depending on testicular differentiation, Müllerian structures may or may not be present. Malignancy risk is high (30–40%) with intra-abdominal gonad, thereby needing gonadectomy in female sex of rearing and in male sex with inability to surgically bring the gonads into the scrotum. Inguinal or scrotal gonads need a close follow-up for malignancy.

Ovotesticular DSD

Ovotesticular DSD is diagnosed when there is presence of ovarian follicles and testicular tissue in the same individual. Demonstration of ovarian stroma is not sufficient to make diagnosis. Karyotype is most commonly 46,XX (nearly 95% in Africa, about 50–70% in Europe and North America). Other karyotypes include

BOX 1 Examples of conditions included in DSD

1. 46,XX DSD
  • Androgen excess
    – Congenital adrenal hyperplasia
      - 21-hydroxylase deficiency
      - 11-hydroxylase deficiency
      - 3β-hydroxysteroid dehydrogenase deficiency
      - P450 oxidoreductase deficiency
    – Placental aromatase deficiency
    – Maternal virilizing tumor
    – Maternal androgenic drugs
  • Disorders of gonadal development
    – Ovotesticular DSD
    – 46,XX testicular DSD (SRY+, SOX9 duplication)
  • Other conditions
    – Cloacal exstrophy
    – Vaginal atresia
    – MURCS syndrome
2. 46,XY DSD
  • Disorders of gonadal development
    – Gonadal dysgenesis (complete or partial)
    – Gonadal regression
    – Ovotesticular DSD
  • Disorders of androgen synthesis or action
    – Smith-Lemli-Opitz syndrome
    – LH receptor mutations
    – StAR deficiency
    – 3β-hydroxysteroid dehydrogenase deficiency
    – 17-hydroxylase/17,20-lyase deficiency
    – P450 oxidoreductase deficiency
    – 17β hydroxysteroid dehydrogenase deficiency
    – 5α-reductase deficiency
    – Androgen insensitivity (complete or partial)
  • Other conditions
    – Persistent Müllerian duct syndrome
3. Sex chromosome DSD
  • 45,X (Turner syndrome and variants)
  • 47,XXY (Klinefelter syndrome and variants)
  • 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
  • 46,XX/46,XY (chimeric, ovotesticular DSD)

Abbreviations: β-HSD, β-hydroxysteroid dehydrogenase; POR, P450 oxidoreductase; DSD, disorders of sexual development; SRY, sex determining region on Y chromosome; LH, luteinizing hormone; StAR, steroidogenic acute regulatory protein; MURCS, Müllerian, renal, cervicothoracic somite abnormalities; SOX9, SRY box 9.

BOX 2 Key management points in 21-hydroxylase deficiency

Patient in crisis:
  – Hospital admission, emergency management of shock, hypoglycemia and hyperkalemia
  – IV fluids (5% dextrose with normal saline)
  – IV hydrocortisone (bolus followed by 6–8 hourly)
  – Monitor glucose, electrolytes, BP, hydration
Long-term management:
  – Oral hydrocortisone (8–20 mg/m^2/day, divided in 3 doses)*
  – Fludrocortisone (0.05–0.3 mg/day, single daily dose in salt wasting form)**
  – Salt supplementation (1–3 g/day, in infancy)
  – Stress dosing of steroids (2–3 times elevated dose for infections, trauma, surgery, parenteral hydrocortisone if oral administration not possible/major surgery)
  – Monitor height, weight, BP, pubertal progression, side effects of treatment
  – Lab tests in follow-up: 17OHP, testosterone, plasma renin activity
  – Imaging for testicular adrenal rest tumors in poorly controlled patients

*Equivalent doses of prednisolone/dexamethasone can be used beyond completion of growth.
**Higher doses required in infants, also useful in simple virilizing form with elevated plasma renin.
Abbreviations: IV, intravenous; BP, blood pressure; 17OHP, 17-hydroxyprogesterone.

46,XX/46,XY chimerism and 46,XY. Gonads may be ovotestis on one side and testis or ovary on the other (50%), ovotestes on both sides (30%) or testis on one side and ovary on other (20%). The ovary is usually in its normal location but testes or ovotestes are most commonly seen in the inguinal region, although can be intra-abdominal or rarely scrotal. External genitalia are ambiguous in most of the cases and variable degree of androgen effect may be seen. Uterus or hemiuterus may be present depending on AMH secretion on that side. Delayed presentations may include gynecomastia or cyclic hematuria in the male. Individuals with a uterus and lack of significant virilization have potential for menstruation and pregnancy if reared as females. Appropriate sex steroid replacement may be required in either sex of rearing. Malignancy risk is low.

Table 4 Enzyme deficiencies associated with 46,XX DSD

Condition	21-hydroxylase deficiency	11β-hydroxylase deficiency	3β-hydroxysteroid dehydrogenase deficiency	P450 oxidoreductase deficiency	Placental aromatase deficiency
Gene	CYP21A2	CYP11B1	HSD3B2	POR	CYP19A1
Chromosome	6p21.1	8q21-22	1p13.1	7q11-12	15q21.2
Inheritance	AR	AR	AR	AR	AR
External genitalia	Ambiguity in females, normal in males	Ambiguity in females, normal in males	Ambiguous in both sexes	Ambiguous in both sexes	Ambiguity in females
Associated features	*Classic form*: Features of glucocorticoid and mineralocorticoid deficiency, ACTH and androgen excess *Simple virilizing*: Only clinical features of ACTH and androgen excess	Low renin hypertension, hypokalemia, ACTH excess	Classic and simple virilizing forms as in 21-hydroxylase deficiency, gynecomastia at puberty in males	Cortisol deficiency, relatively preserved mineralocorticoid function, skeletal features of Antley-Bixler syndrome	Progressive maternal virilization, delayed puberty, multiple cysts in ovary
Diagnostic hormone profile	Massive elevations in 17OHP (usually > 100 ng/mL)	Elevated 17OHP (lesser extent than 21-hydroxylase), elevated deoxycortisol, DOC	Elevated Δ5/Δ4 steroids (elevated pregnenolone, 17-OH pregnenolone, DHEA)	Elevated progesterone, 17OHP, features of combined 21- and 17-hydroxylase deficiency, low estradiol	Elevated androstenedione, testosterone, low estrone and estradiol

Abbreviations: AR, autosomal recessive; DOC, deoxycorticosterone; 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone.

Table 5 Important genes associated with 46,XY gonadal dysgenesis

Gene	Chromosome locations	Clinical presentation
WT1	11p13	WAGR syndrome, Frasier syndrome, Denys-Drash syndrome
SF1	9q33	Gonadal dysgenesis, adrenal hypoplasia, hypogonadotropic hypogonadism
SRY	Yp11.3	Mutations and deletions: XY gonadal dysgenesis Translocation to X: XX, testicular DSD
SOX9	17q24	Campomelic dysplasia, gonadal dysgenesis
DAX1	Xp21.3	*Deletions*: Hypogonadotropic hypogonadism, adrenal insufficiency *Duplication*: XY gonadal dysgenesis

Table 6 Disorders of androgen biosynthesis (also see Box 2)

Condition	LH/hCG receptor	StAR deficiency	17-hydroxylase/17,20-lyase deficiency	17β-HSD deficiency	5α-reductase deficiency
Gene	LH/hCGR	STAR	CYP17A1	HSD17B3	SRD5A2
Chromosome	2p21	8p11.2	10q24.3	9q22	2p23
Inheritance	AR	AR	AR	AR	AR
Clinical features	Female appearing external genitalia in complete form, ambiguity in partial	More common in Japan and Korea, female external genitalia in males, no ambiguity in females	Female/ambiguous genitalia in males, normal in females, sparse axillary/pubic hairs in both sexes, hypergonadotropic hypogonadism	Female/ambiguous genitalia in males, normal in females, separate urethra and vaginal opening, blind vaginal pouch	Variable degree of undervirilization
Adrenal steroids	Not affected	Severe adrenal insufficiency in infancy, lipoid adrenal hyperplasia	Excess DOC, impaired androgen and estrogen production, low renin hypertension, hypokalemic alkalosis, excess corticosterone exerts some glucocorticoid action	Normal cortisol, aldosterone and DHEA	Normal
Biochemical profile	Elevated LH, low T, poor T response to hCG stimulation	Low serum and urinary steroids (all steroids)	Low plasma renin, elevated DOC, hypokalemia, alkalosis	T/A ratio < 0.8	Increased ratio of T/DHT, decreased 5α/5β C21 and C19 urine steroids
Changes at puberty	Lack of spontaneous puberty	Hypergonadotropic hypogonadism in both sexes	Delayed puberty in both sexes, gynecomastia in males	Virilization at puberty, gynecomastia variable	Virlization at puberty, no gynecomastia

Abbreviations: LH, luteinizing hormone; hCG, human chorionic gonadotropin; AR, autosomal recessive; DHEA, dehydroepiandrosterone; DOC, deoxycorticosterone; T, testosterone; A, androstenedione; DHT, dihydrotestosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; StAR, steroidogenic acute regulatory protein.

RECOGNITION OF ATYPICAL GENITALIA

Examination of external genitalia should be a mandatory part of newborn examination. Timely detection of hyperpigmentation and absence of palpable testes in an apparent male may avert fatal outcomes in CAH. Delay in recognition may also lead to wrong sex assignment causing distress to parents and significant social complications. In developing countries delayed presentations are very common, therefore leading to highly variable clinical presentation **(Table 7)**.

Clinical Evaluation

History
Privacy and confidentiality of patients and family should be strictly observed during the entire process of evaluation. Specific points to be noted in the history include:

- Detailed history of pregnancy including signs of virilization in mother (virilizing tumors, placental aromatase deficiency), medication use (androgenic progestins, danazol, antiandrogens).

- A pedigree chart should be used to take history of at least three generations for any consanguinity, family history of DSD, primary amenorrhea or infertility, neonatal deaths.
- Symptoms of glucocorticoid deficiency, mineralocorticoid deficiency or excess and ACTH excess **(Fig. 2)**.
- Gender role and identity should be explored, as should sexual preferences in adolescents, cultural and family background and presence of psychological problems.
- Assessment for other organ anomalies and developmental delay to rule out syndromic associations **(Table 8)**.

Examination
General examination consists of assessment of hydration status, weight, blood pressure, skin and mucosal pigmentation, presence of dysmorphic features and skeletal deformities (*SOX9* mutations causing campomelic dysplasia and POR deficiency with Antley-Bixler syndrome). Careful inspection of genitalia should be done to evaluate presence of gonads, pigmentation of labioscrotal skin, rugosity and symmetry of external genitalia **(Figs 3A and B)**. Asymmetry is common in XY gonadal dysgenesis, partial androgen

Table 7 Clinical presentations of DSD

Presentations in infancy	
Apparent male child with: • Bilateral undescended testes • Micropenis • Severe degrees of hypospadias • Mild hypospadias with micropenis/cryptorchidism • Partially fused labioscrotal folds (giving appearance of bifid scrotum) • Presence of uterus	*Apparent female child with:* • Palpable gonad in inguinal/labial region • Enlarged clitoris (sometimes giving appearance of penis) • Lack of separate urethral and vaginal opening • Fusion of labioscrotal folds
Delayed presentations	
• Previously unrecognized genital ambiguity (all presentations listed above) • Peripheral precocious puberty • Acute/chronic adrenocortical insufficiency • Delayed puberty • Primary amenorrhea • Gynecomastia • Virilization in a female (hirsutism, clitoromegaly) • Gross and cyclic hematuria in a male • Hypertension (with mineralocorticoid excess)	

Figure 2 Symptoms of congenital adrenal hyperplasia

insensitivity and ovotesticular DSD. Hypospadias, if present, should be further described as per the location of the urethral meatus (glanular, also called glandular, subcoronal and penile are the most distal, moving with severity of hypospadias to penoscrotal and perineal). Labioscrotal folds are assessed for the degree of fusion which is classified as no fusion, posterior fusion, partially fused hemiscrotum and fully fused scrotum. Anogenital ratio (distance between anus to posterior fourchette/distance between anus and base of phallus) greater than 0.5 indicates fusion of labioscrotal folds.

Prader staging **(Fig. 4)** is used to describe the extent of virilization of external genitalia with stage 1 representing clitoromegaly (most female appearing) and stage 5 being isolated hypospadias (most male appearing). External masculinization score can be calculated **(Fig. 5)**; a score of less than 11 indicates a need for evaluation in an apparent male.

Gonads should be palpated between thumb and other fingers in inguinal or labioscrotal area and are more easily found in standing or squatting position. A palpable gonad is a testis unless proven otherwise. Stretched phallic length should be taken from pubic ramus to tip of phallus excluding foreskin. In the newborn, a length of less than 2 cm is consistent with micropenis and clitoral length of greater than 1 cm with clitoromegaly. Some degree of clitoromegaly can be present in preterm newborns; hence, the diagnosis of CAH should be made only in consultation with a pediatric endocrinologist in preterm babies.

Investigations
It is not necessary to do all tests in all the patients. Isolated unilateral inguinal testes or isolated glandular or coronal hypospadias do not merit extensive investigations.

Karyotype
In most of the cases a peripheral blood karyotype is sufficient, however rarely skin and gonadal biopsies may be required to rule out mosaicism. FISH using X and Y specific probes may give rapid information but should be followed by formal karyotype.

Table 8 Dysmorphic syndromes with atypical genitalia

Syndrome	*Clinical features*
Smith-Lemli-Opitz syndrome	Microcephaly, mental retardation, cardiac defects, ptosis, upturned nose, micrognathia, cleft palate, polydactyly, syndactyly of toes (especially, the second and third toes), severe hypospadias, micropenis and growth failure
WAGR syndrome	Wilms tumor, aniridia, cataracts, genitourinary abnormalities, mental retardation
CHARGE syndrome	Coloboma, heart defect, choanal atresia, retarded growth, genital hypoplasia, ear anomalies
Robinow syndrome	Flat facies, hypertelorism, hypoplastic genitalia, frontal bossing, long philtrum, triangular mouth with downturned angles, hemivertebrae of thoracic vertebrae
X-linked lissencephaly	Lissencephaly, genital ambiguity
Trisomy 13 (Patau syndrome)	Holoprosencephaly, polydactyly, cleft lip, hypospadias, cryptorchidism

Figures 3A and B (A) External genitalia examination illustrates micropenis, chordee, proximal penile hypospadias, bilateral cryptorchidism and poorly formed scrotum without rugosities. The child had XY gonadal dysgenesis; (B) External genitalia revealing the scrotal sacs to have well formed rugosities, but no gonads. The baby had congenital adrenal hyperplasia in a genotypic girl with karyoptype 46,XX
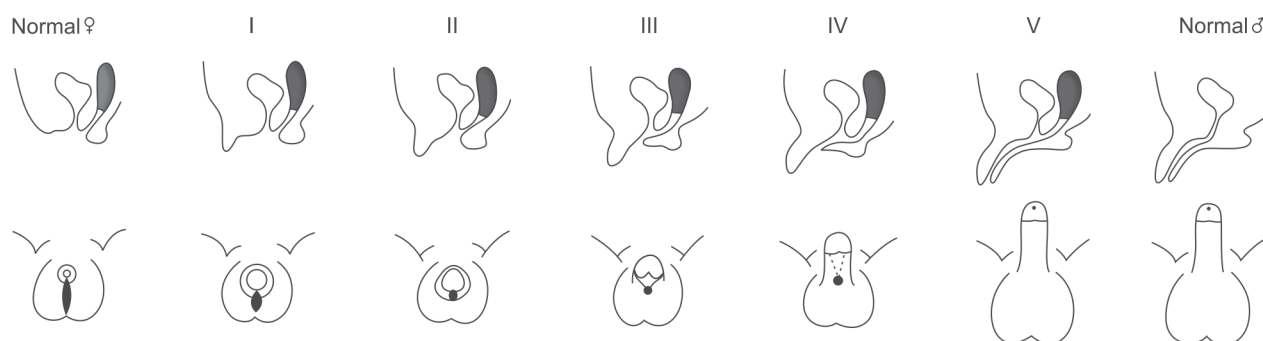
Figure 4 Prader staging of external genitalia
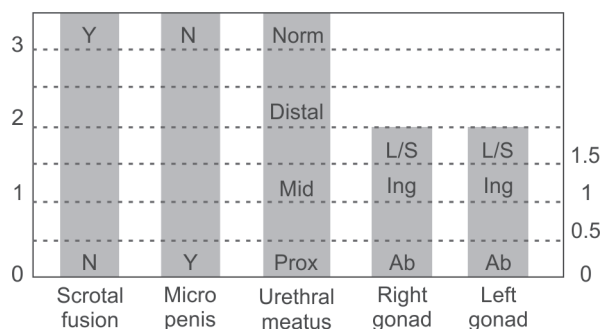
Figure 5 External masculinization score
Abbreviations: L/S, labioscrotal; Ing, inguinal; Ab, absent.

Defining Internal Anatomy

It is necessary to define the presence of Müllerian structures, to locate gonads if not palpable externally and to define the degree of fusion of urethra and vagina. An ultrasound of the pelvis can detect the presence of inguinal gonads and visualize the uterus. Second line investigations to define internal anatomy include MRI of pelvis and diagnostic laparoscopy. The latter is also useful for taking gonadal biopsies to determine histology. Cystoscopy is useful to determine the degree of fusion of urethra and vagina.

Hormonal Studies

17-hydroxyprogesterone (17OHP) levels can be determined in all cases as the most common cause of genital ambiguity is 21-hydroxylase deficiency. In infants with palpable gonads, baseline LH, follicle stimulating hormone (FSH) and total testosterone (after hCG stimulation if the child is past the age of neonatal minipuberty but is not yet pubertal) should be done on a morning sample. AMH is gaining popularity as a reliable marker of sertoli cell function. Levels even at birth are well above the female levels in the presence of functional testes.

Urine Steroid Profile

All steroids are metabolized and excreted in urine. Urinary gas chromatography mass spectrometry (GCMS) for analysis of ratios of urinary steroid metabolites is emerging as an investigation of choice in various types of CAH, 5α-reductase deficiency and 17β-HSD deficiency.

Gonadal Biopsies

Gonadal biopsies are essential to establish the diagnosis of dysgenesis and ovotesticular DSD.

APPROACH TO THE DIAGNOSIS

Genital ambiguity needs to be differentiated from normal variations like apparent clitoromegaly in the preterm, isolated labial adhesions and isolated glandular hypospadias. In all patients meeting the criteria for DSD, karyotype, ultrasound of pelvis, sodium, potassium, glucose and 17OHP should be done. If facilities for endocrine testing are unavailable, a clinical suspicion of CAH should be followed by collection and storage of a serum sample (for future analysis) and subsequent presumptive

treatment. Further testing depends on outcome of these initial tests and as per clinical features as mentioned in algorithms 1 and 2 **(Flow charts 3 and 4)**. Maximum efforts should be made to make a specific diagnosis which may require additional tests like an ACTH stimulation test, urine steroid profile or genetic testing.

MANAGEMENT

Management of children with DSD is aimed at achieving normal functioning in society. Goals include sex assignment as male or female, phenotypic and psychological outcomes concordant with assigned sex, achievement of normal sexual function and

Flow chart 3 Algorithm 1: evaluation of DSD with no palpable gonads

*usually at least one gonad is palpable
Abbreviations: DSD, disorders of sexual development; 17OHP, 17-hydroxy-progesterone; CAH, congenital adrenal hyperplasia.

efforts to achieve fertility. A multispecialty team offers the best hope of a cohesive management plan. Sensitive and effective counseling of the parents is must. Analogies of common congenital malformations and pictorial explanations of genital development can be used to explain the condition.

Sex of Rearing

Hasty decisions need to be avoided. Factors to be considered include the underlying cause of DSD, appearance of external genitalia and internal anatomy, potential for sexual function, potential for fertility, need for hormone replacement, family beliefs and cultural practices and the feasibility of surgical correction. In addition, in cases presenting late, gender identity, gender role and preferences of the patient also need to be considered.

Based on data of gender identity, 46,XX infants with CAH are raised as females despite severe virilization. Those presenting in late childhood or adolescence with male like external genitalia and male gender identity may be occasional exceptions. Individuals with 46,XY complete androgen insensitivity syndrome (CAIS) are raised as females as androgen resistance at the brain prevents male gender identity. In other cases, individualized decisions need to be made. More than half of 5α-reductase deficiency and 17β-HSD3 patients identify themselves as males and virilize at puberty, hence these facts merit consideration during decision-making regarding sex of rearing in these conditions.

Medical Management

Infant with salt wasting CAH should be admitted and treated with hydrocortisone, fludrocortisone and salt supplementation. The details are highlighted in chapter 44.15. Infants with micropenis and 46,XY DSD reared as males are usually given injection, testosterone enanthate 25 mg once a month intramuscular for 3 months. A positive response indicates androgen responsiveness and improves cosmetic appearance and urinary stream in boys. Appropriate sex steroid replacement needs to be started at the pubertal age in conditions where spontaneous development does not occur.
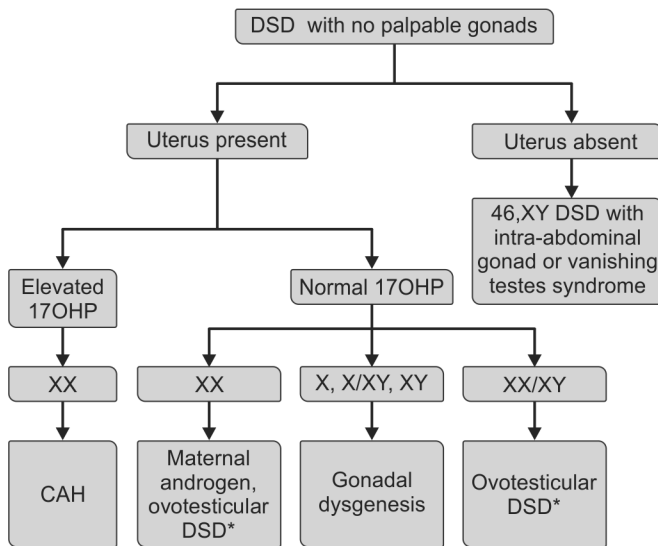
Flow chart 4 Algorithm 2: evaluation of DSD with at least one palpable gonad
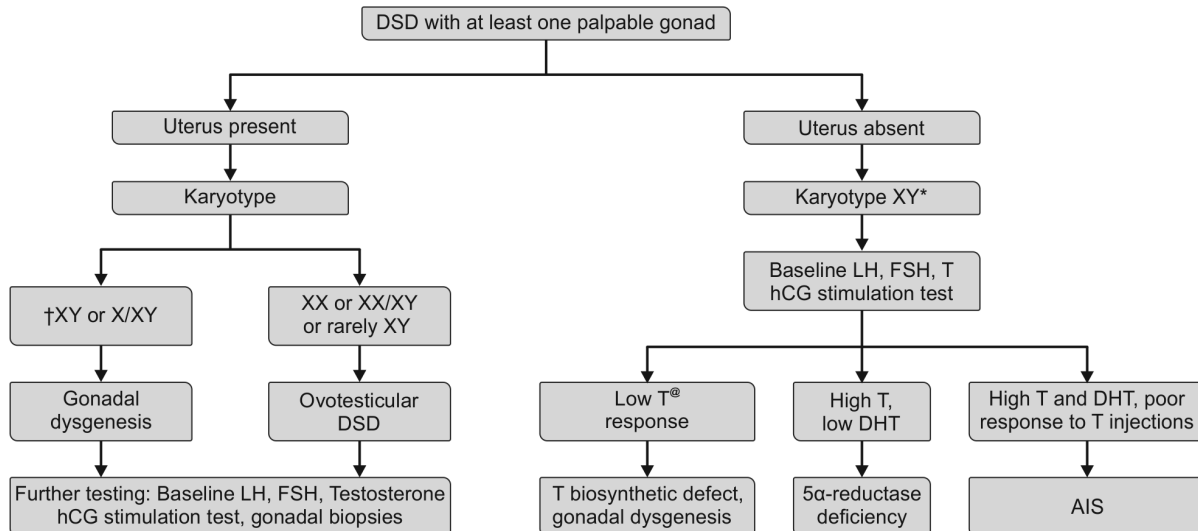
* 46,XX with absent uterus and palpable gonad may suggest 46,XX testicular DSD (XX male).
@ Prolonged hCG stimulation test may be required to confirm.
† Uterus may be present in persistent Müllerian duct syndrome, but external genitalia are normal male.
Abbreviations: LH, luteinizing hormone; FSH, follicle stimulating hormone; T, testosterone; hCG, human chorionic gonadotropin; DHT, dihydrotestosterone; AIS, androgen insensitivity syndrome.

Surgical Management

The decision for surgery needs to be individualized. Mild or moderate degree of clitoromegaly may regress with steroid treatment in CAH. Higher degrees of urogenital fusion needs to be treated surgically, especially to reduce urinary reflux and repeated urinary tract infection (UTI). Reduction clitoroplasty when performed should preserve the neurovascular bundle to maintain sexual sensitivity. Gonadectomy is performed in 46,XY DSD raised as females. With high-risk of malignancy in gonadal dysgenesis with nonscrotal gonad, it is performed at early age, whereas in CAIS, it is deferred till adolescence as breast development by aromatization of testosterone to estrogen is better than exogenous estrogen supplementation. In children with androgen biosynthetic defects raised as females, gonadectomy is performed prior to puberty to avoid risk of virilization.

In male sex of rearing, surgical procedures include orchiopexy, chordee corrections, hypospadias repair and sometimes müllerectomy. Severe degrees of hypospadias often need repair in multiple stages. This is preferably done between 6 months and 24 months of age. Inguinal and scrotal testis in dysgenesis needs to be periodically evaluated for malignancy by palpation and ultrasound.

Genetic Counseling

All patients with DSD must be offered genetic counseling and family screening as a chance of recurrence is there in 25% of all pregnancies in autosomal recessive conditions and all male infants in X-linked recessive conditions.

Psychological Support

Understandably, there are significant psychological issues in DSD throughout life and regular psychological evaluation and counseling, as well as patient support groups are necessary parts of management.

Risk of Malignancy

Malignancy risk is high (20–50%) in intra-abdominal gonad with Y chromosome material in cases of gonadal dysgenesis, Frasier syndrome, partial androgen insensitivity syndrome (PAIS) and Denys-Drash syndrome. It is low in ovotesticular DSD and CAIS. Carcinoma in situ and gonadoblastoma may occur and also invasive tumors like dysgerminoma and seminoma are likely.

IN A NUTSHELL

1. Knowledge of gonadal development, differentiation of internal and external genitalia from bipotential structures of embryonic life and steps involved in steroidogenesis are critical to the understanding of DSD.
2. In newborns presenting with bilateral cryptorchidism or genital ambiguity, early evaluation is aimed at ruling out CAH.
3. A stepwise approach including history, examination and judicious use of investigations is necessary. Increasing international cooperation in the field of endocrinology has improved availability of tests like urine steroid profile and genetic studies.
4. Communication with the family is of prime importance and should be done by an experienced team with appropriate protocols.

MORE ON THIS TOPIC

Ahmed SF, Achermann JC, Arlt W, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol. 2011;75:12-26.

Ammini AC, Gupta R, Kapoor A, et al. Etiology, clinical profile, gender identity and long-term follow-up of patients with ambiguous genitalia in India. J Pediatr Endocrinol Metab. 2002;15:423-30.

Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006;118:e488-500.

Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia. Arch Dis Child. 2004;89:401-7.

Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab. 2011;25:221-38.

Chapter 44.21
Cryptorchidism and Micropenis
Aparna Limaye

CRYPTORCHIDISM

Cryptorchidism is a major cause of infertility and is associated with a higher incidence of germ cell tumors. Its literal meaning is hidden or obscure testes. Many aspects of this condition are still not clearly elucidated despite intensive research for over 100 years.

EPIDEMIOLOGY

Overall 3% of all full-term newborn males have undescended testes, decreasing to 1% by the age of 6 months to 1 year. Since transinguinal descent begins only by the 7th month of gestation, preterms have an incidence of 30% at birth. It is unilateral in 70% with right side more often affected. The incidence is increasing probably due to increased exposure to environmental chemicals and estrogen.

PATHOPHYSIOLOGY

The presence of *SRY* (*sex determining region of Y*) and factors steroidogenic factor 1 (*SF1*), Wilms tumor suppressor gene (*WT1*) are required for testicular differentiation. Sertoli cells start producing Anti-Müllerian hormone (AMH) at 6 weeks causing Müllerian structures to regress. By 9 weeks, Leydig cells start producing testosterone initially under placental human chorionic gonadotropin (hCG) stimulation and after 14 weeks due to fetal pituitary stimulation, leading to Wolffian duct maturation. There are two stages of testicular descent:

1. *8–15 weeks–transabdominal phase*: The testes remain suspended between the cranial suspensory ligament (CSL) and the caudal gubernaculum. Leydig cells produce insulin-like factor 3 (INSL3) which acts on the leucine-rich repeat containing G-protein-coupled receptor 8 (LGR8) receptor on the gubernaculum causing it to grow and become thicker. The testes remain tethered to the future inguinal region as the fetal abdomen grows. Mutations of *INSL3* and *LGR8* genes have been identified in patients with cryptorchidism. Differential growth of vertebrae and pelvis until 23 weeks of gestation contributes to transabdominal descent. Disorders affecting this stage often results in bilateral cryptorchidism.

2. *25–35 weeks–transinguinal phase*: Migration of testes from the inguinal region to the scrotum is facilitated by development of gubernaculum, processus vaginalis and spermatic vessels. The genitofemoral nerve releases calcitonin gene-related peptide (CGRP), a neurotransmitter that provides a chemotactic gradient to guide this migration. Androgen (testosterone and dihydrotestosterone) production and action are required for this migration and hence a normal hypothalamic-pituitary-gonadal axis is a prerequisite. Patients with 5α-reductase deficiency and partial androgen insensitivity can complete the intra-abdominal phase but fail to undergo inguinoscrotal descent. Disorders affecting this phase often result in unilateral undescended testes.

ETIOLOGY

The etiology is multifactorial. Extensive research has implicated some factors but exact mechanism remains elusive.

- *Birth weight* is a major determinant irrespective of gestational age.
- *Familial predisposition*: About 23% of index patients have a positive family history as opposed to 7.5% in control families. The risk is 7 and 4 times respectively if sibling and father affected.
- *Intra-abdominal pressure* plays an important role as conditions such as prune-belly syndrome, cloacal exstrophy, omphalocele are associated with an increased incidence.
- *The gubernaculum* plays a significant role; both mechanical and hormonal factors are involved. It is not firmly attached to the scrotum in cases of cryptorchidism and hence testes are not pulled into the scrotum. Its development depends on INSL3 acting through the LGR8 receptor. CGRP secreted by the genitofemoral nerve aids in gubernacular descent.
- *Endocrine causes* are found in only a small proportion. Multiple pituitary hormone deficiencies, isolated growth hormone (GH) deficiency, disorders of androgen production and action can cause undescended testes.
- *Dysmorphic syndromes*: Down, Klinefelter, Noonan and Prader-Willi syndromes are associated with cryptorchidism.

COMPLICATIONS

There are two critical prepubertal steps involved in the maturation or proliferation of germ cells. At 2–3 months of age, transformation of fetal stem cell pool into adult stem cell pool [adult dark (Ad) spermatogonia] takes place due to the luteinizing hormone (LH) and follicle stimulating hormone (FSH) surge (mini puberty), at the right temperature. At 4–5 years, these spermatogonia are transformed into primary spermatocytes. Infertility results if there is a delay in treatment—33% in unilateral cases, 66% in bilateral cryptorchidism. There is a 40% increased risk of testicular cancer; seminoma is the most common tumor in untreated testes. Malignant transformation occurs after puberty, peak age being 15–40 years. A patent processus vaginalis, predisposing to hernia, is present in 90% patients.

APPROACH TO MANAGEMENT

- *History*: History should be sought regarding birth weight, gestational age and hypoglycemia in the newborn period, mother's diet, family history of genitourinary abnormalities, infertility, consanguinity, disorder of sex development (DSD) and infant deaths. A history of previously palpable testes and history of inguinal surgery in older children are important.
- *Clinical examination*: A search for associated dysmorphisms, midline defects and nystagmus is important. Other malfor-mations such as imperforate anus, esophageal atresia, neural tube defects and ventricular septal defects are seen with higher frequency (46%) in bilateral cryptorchidism as compared to unilateral undescended testes (10%).
- *Genital examination*: Documentation of hyperpigmentation, location of the urethral opening, bifidity and rugosity of the scrotum, hypertrophy of the contralateral descended testis, penile length and chordee is important. Patient has to be warm and relaxed. Frog leg or squatting position is preferred. With warm or soapy hands, palpate for gonads from the iliac crest to the scrotum.

Undescended testes can be truly undescended, retractile or ectopic. Retractile testes are found in 20% normal boys between the ages 1 year and 5 years and are due to a hyperactive cremasteric reflex. There is a 50% risk of ascent. Ectopic testes (5–10%) exit the external inguinal ring but get misdirected into the superficial inguinal pouch, femoral or perineal region. Both conditions have better therapeutic and prognostic implications. 20% of all cryptorchidism are truly nonpalpable as they are intra-abdominal or absent. Vanishing testes (3%) occur due to in utero torsion of testicular vessels after 14th week of gestation. *No*

work-up is required in case of unilateral undescended testis without hypospadias.

Laboratory Work-up

Karyotyping is mandatory to rule out a DSD. **Table 1** highlights the hormonal work-up which may be needed. Elevated LH and FSH levels and poor testosterone response to hCG stimulation suggest anorchia. Alternatively, sertoli cell markers like AMH and inhibin B can be used to determine presence of functioning testes. AMH levels are high during first 6 years of life (20–80 ng/mL). Low levels of inhibin B and high FSH levels in patients with cryptorchidism serve as predictors of impaired spermatogenesis in later life.

Radiological Studies

Ultrasound, CT scan and MRI have only 44% accuracy in localizing undescended testes. Magnetic resonance angiography has 100% sensitivity but is expensive. Diagnostic laparoscopy is the modality of choice. In cases of DSD (see Chapter 44.20), ultrasonography and genitography are indicated.

TREATMENT

The expected benefits of early treatment include a higher likelihood of fertility, facilitation of testicular examination and reduced risk of malignancy, correction of associated hernia, prevention of testicular injury against pubic bone or torsion and prevention of psychological stress caused by an empty scrotum.

Medical Therapy

The age of treatment of cryptorchidism has been pushed up over recent years to 6 months as the chances of spontaneous descent are rare after 6 months and there is a higher possibility that fertility may improve with early intervention. Patient selection is crucial as distally located testes are more likely to descend than intra-abdominal testes. hCG (the action is identical to pituitary LH and stimulates Leydig cells to produce androgens and facilitates descent) or gonadotropin-releasing hormone (GnRH) analogs (the initial agonistic effect stimulates the release of pituitary gonadotropins and increases gonadal steroidogenesis) may be tried in cases of palpable poorly descended testes.

Surgical Therapy

Early surgery (orchiopexy) is advocated between 6 months and 1 year of age since spontaneous descent rare after 6 months of age. Successful surgical placement in the scrotum requires adequate mobilization of the testes and spermatic vessels, ligation of the associated hernia sac and adequate fixation in a dependent portion of the scrotum. Orchiectomy is recommended in case of intra-abdominal dysgenetic testes.

Table 1 Hormonal work-up in cryptorchidism

Etiology	Test
Dysmorphic syndromes	Specific gene mutation, karyotype
Hypopituitarism	Serum cortisol, GH, free T4, urine osmolality, LH, FSH
Defective testosterone synthesis	hCG stimulation test to look for T response
Defective testosterone action	hCG stimulation test, T/DHT ratio

Abbreviations: GH, growth hormone; T4, thyroxine; LH, luteinizing hormone; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; T, testosterone; DHT, dihydrotesterone.

MICROPENIS

Micropenis refers to a normally formed penis which is less than 2.5 standard deviations (SD) below the mean. If there is associated severe degree hypospadias, the term microphallus is used as it could represent a small penis or an enlarged clitoris. Mean stretched penile length (SPL) for a full term newborn male is 3.5 cm. Very little penile growth occurs after the first year of life till puberty when it resumes because of increased testosterone production. Penile length less than 2.5 cm in a neonate and 4 cm in an older boy is considered abnormal.

ETIOLOGY

The most common cause is deficiency of testosterone secondary to abnormal pituitary function, followed by primary testicular disorders and syndromic conditions. However, the most common consultation to a pediatrician for micropenis will be in the context of an obese boy brought for evaluation of apparently small genitalia. No endocrine evaluation is required as the penis is generally of normal length and the apparent smallness is due to the penis being concealed in the suprapubic pad of fat.

Hypogonadotropic Hypogonadism (Low LH, FSH and Testosterone)

Conditions included in this category are Kallmann syndrome (associated with anosmia), normosmic hypogonadotropic hypogonadism and multiple pituitary hormone deficiencies. It may be secondary to transcription factor mutations (PROP1, LHX3, XESX1 mutations) (see also Chapter 44.11 on Delayed Puberty).

Hypergonadotropic Hypogonadism (High LH, FSH and Low Testosterone)

Testicular degeneration due to torsion or vaso-occlusive event in utero leads to anorchia. Testicular degeneration after 14 weeks of gestation causes isolated micropenis with bilateral undescended testes. Defects in testosterone steroidogenesis and testosterone action can present with micropenis, but they are usually in the context of other major external genitalia abnormalities like a severe degree of hypospadias with or without bilateral cryptorchidism (see also Chapter 44.20 on DSD).

Genetic Syndromes

Klinefelter syndrome and other poly X syndromes have hyper-gonadotropic hypogonadism. Prader-Willi syndrome manifests in males as cryptorchidism, an underdeveloped scrotum and micropenis. Bardet-Biedl (polydactyly and retinitis pigmentosa), Noonan (having dysmorphic features resembling Turner syndrome) and CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndromes may all be associated with micropenis.

CLINICAL FEATURES AND APPROACH

History and Physical Examination

Table 2 highlights important points to be noted in the history. Physical examination should include a search for midline defects, visual defects and anosmia, documentation of growth velocity, hyperpigmentation and failure to thrive. Genital examination to confirm the presence of micropenis should be performed by grasping the glans between thumb and forefinger and fully stretching the phallus along a firm ruler at a right angle to the pubic symphysis. The length is measured along the dorsum from the base to the tip of the glans, taking care to push back the pubic pad of fat.

Table 2 Clinical work-up of micropenis

Family history of unexplained infantile deaths	Defects in steroidogenesis: salt-wasting CAH
Family history of genital ambiguity	5α-reductase deficiency, PAIS
Family history of consanguinity and females undergoing marked virilization at puberty	5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency
Breech delivery, neonatal jaundice, poor linear growth	Hypopituitarism
Failure to thrive, hyperpigmentation	Defects in steroidogenesis

Abbreviations: CAH, congenital adrenal hyperplasia; PAIS, partial androgen insensitivity syndrome.

Investigations

A karyotype will help to confirm chromosomal sex (normal male or female or Klinefelter karyotype) and to evaluate genetic syndromes like Prader-Willi. LH and FSH levels peak in the first few months of life and can be used to differentiate between hypogonadotropic and hypergonadotropic hypogonadism. In case of suspected hypopituitarism, blood glucose, free thyroxine (T4), cortisol and GH should also be evaluated. The work-up of patients with genital ambiguity is described in detail in Chapter 44.20.

TREATMENT

The aim is to treat the underlying cause and achieve adequate penile growth. Most cases are due to testosterone deficiency and hence testosterone therapy is the mainstay of treatment. In infants, 2–3 injections of testosterone (25 mg given IM every 4 weeks) should result in adequate penile growth. With appropriate pubertal and adult replacement, normal adult penile size and function can be achieved though infertility is generally expected. Transdermal dihydrotestosterone is effective in 5α-reductase deficiency. Other hormone replacements are necessary in hypopituitarism. Later if fertility is desired, hCG and recombinant FSH can be given to promote spermatogenesis. Circumcision is to be avoided or delayed till appropriate penile length is achieved.

MORE ON THIS TOPIC

Ashley RA, Barthold JS, Kolon TF. Cryptorchidism: pathogenesis, diagnosis, treatment and prognosis. Urol Clin North Am. 2010;37:183-93.

Chul Kim S, Kyoung Kwon S, Pyo Hong Y. Trends in the incidence of cryptorchidism and hypospadias of registry-based data in Korea: a comparison between industrialized areas of petrochemical estates and non-industrialized area. Asia J Androlo. 2011;13:715-8.

Cohee L. Endocrinology: Chapter 10; Table 10-19: Mean stretched penile length. In: MM Tschudy, KM Arcara. The Harriet Lane Handbook. 19th ed. Philadelphia: Elsevier; 2012.

Hutson JM, Balic A, Nation T, et al. Cryptorchidism. Semin Pediatr Surg. 2010;19:215-24.

Iwatsuki S, Kojima Y, Mizuno K, et al. Endocrine assessment of prepubertal boys with a history of cryptorchidism and/or hypospadias: a pilot study. J Urol. 2011;185:2444-50.

Penson D, Krishnaswami S, Jules A, McPheeters ML. Effectiveness of hormonal and surgical therapies for cryptorchidism; a systematic review. Pediatrics. 2013;131:e1897-907.

Simon A, Menon PSN. Undescended testes. In: Desai MP, Menon PSN, Bhatia V. Pediatric Endocrine Disorders. Mumbai: University Press; 2014. pp. 293-8.

Tuladhar R, Davis PG, Batch J, Doyle LW. Establishment of a normal range of penile length in preterm infants. J Pediatr Child Health. 1998;34:471-3.

IN A NUTSHELL

1. Bilateral cryptorchidism could herald a genotypic female baby with virilized genitalia due to congenital adrenal hyperplasia. Work-up to rule out this condition deserves urgent attention, to avert a life-threatening emergency.

2. Cryptorchidism is the most common genital problem in pediatrics which if left untreated has clearly deleterious effects. Early recognition and surgery before 1 year of age can reduce impairment of infertility and risk of testicular cancer.

3. Endocrine evaluation is required for all cases of bilateral undescended testes and unilateral or bilateral undescended testes with hypospadias. No work-up is required for isolated unilateral undescended testes without hypospadias.

4. It is important to differentiate true undescended testes from ectopic or retractile testes as the therapeutic and prognostic implications are very different.

5. Though retractile testes are considered a normal variant, children should be monitored regularly till puberty as there is 50% risk of ascent.

6. Patients should be taught testicular self-examination at puberty. Potential issues such as fertility and testicular cancer should be addressed at puberty.

7. Obese boys are often brought for evaluation of *small genitalia;* the apparent smallness is due to the penis being concealed in the suprapubic pad of fat.

8. All newborns with micropenis should be evaluated for life-threatening conditions such as congenital adrenal hyper-plasia (CAH), GH deficiency, adrenocorticotropic hormone (ACTH) deficiency.

9. The important etiologies for isolated micropenis are hypogonadotropic hypogonadism (either isolated or as a part of multiple pituitary hormone deficiency) and Klinefelter syndrome.

Chapter 44.22
Classification of Diabetes Mellitus
Aspi Irani

Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia due to a defect of insulin secretion and/or action, with differing modes of presentation, course and therapy. DM is classified according to the etiology and according to the stage of the disease.

ETIOLOGIC CLASSIFICATION

This has been changing over time as newer knowledge is acquired. The American Diabetes Association (ADA) has classified DM in 4 categories **(Table 1)**. The first two categories, type 1 diabetes mellitus (T1DM), and to a lesser extent, type 2 diabetes mellitus (T2DM) account for majority of cases seen in pediatric population. The third category (*other specific types of DM*) includes eight subgroups; these are rare entities but the pediatrician should be aware of them. The fourth category is *gestational diabetes*. Etiological classification is important for appropriate management and counseling, and for judging the prognosis. The distinction may not always be clear cut; a patient may be assigned to a particular type of diabetes at the time of presentation, but subsequent observation and events may necessitate a revision in the diagnostic category.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus was earlier referred to as *insulin-dependent diabetes* or *juvenile-onset diabetes*. These terms have been discarded as T2DM may also require insulin in later stages and T1DM too can occur in older age groups. T1DM is a chronic autoimmune disease with acute clinical presentation and immediate insulin requirement for survival. It is characterized by selective destruction of the pancreatic beta cells in the islets of Langerhans. In 95% of cases (termed type 1A DM) evidence of autoimmunity can be found at presentation, in the form of islet cell antibodies (ICA), insulin autoantibodies (IAA), antibodies to glutamic acid decarboxylase (GAD65) and to insulinoma-associated antigen 2 (IA-2). In 5% of cases there is no evidence of autoimmunity and no other definable cause for beta cell failure; these are labeled as idiopathic or type 1B DM. As newer autoantibodies are discovered, some cases of type 1B DM may be reclassified as type 1A DM. In a recent study 26% of patients labeled as type 1B DM had a novel islet antigen, zinc transporter 8 (ZnT8). T1DM has strong HLA associations some of which predispose to the disease while others are protective. The duration of symptoms prior to diagnosis is usually short; the patient is ketosis prone, lean, and presents with weight loss (evidences of catabolic state). Patients with T1DM and their family members are more prone to other autoimmune diseases: autoimmune thyroid disease (AITD), celiac disease (CD), pernicious anemia, Addison disease, vitiligo, alopecia areata and autoimmune hepatitis.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus was earlier referred to as *noninsulin dependent diabetes mellitus* or *maturity onset diabetes*. This variety of diabetes is due to a combination of insulin resistance (from obesity, sedentary lifestyle and/or genetic factors) with relative insulin deficiency. Absence of pancreatic autoimmunity and nil or late insulin requirement are important characteristics. It is common in adults though the incidence in adolescent age group has been rising at an alarming rate; in some centers over 50% of new onset diabetes in adolescents is T2DM. Typically, onset and progression of symptoms is slow and ketosis is uncommon but presentation with ketoacidosis should not be held as a point against the diagnosis. Patients often have a family history of T2DM, may be overtly obese or have increased abdominal fat, may have hypertension, acanthosis, dyslipidemia and in females there may be signs of polycystic ovarian disease (PCOD) **(Table 2)**. The insulin levels are high or in normal range but below the expected for level of blood glucose (BG).

Table 1 Etiologic classification of diabetes mellitus

Category of diabetes	Subgroups (with some examples)
Type 1 diabetes (destruction of beta cells with absolute insulin deficiency)	1A: Autoimmune 1B: Idiopathic
Type 2 diabetes (due to combination of insulin resistance with relative insulin deficiency in varying proportions)	
Other specific types of diabetes	1. *Genetic defects of beta cell function*: Neonatal DM, MODY, Wolfram syndrome, Roger syndrome, Mitochondrial DM 2. *Genetic defects in insulin action*: Type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome, Lipoatrophy syndromes 3. *Disorders of exocrine pancreas*: FCPD, cystic fibrosis, chronic pancreatitis, autoimmune pancreatitis, hemosiderosis, beta-thalassemia, alpha-1-antitrypsin deficiency, pancreatectomy 4. *Endocrinopathies*: Cushing syndrome, hyperthyroidism, pheochromocytoma, etc. 5. *Drug or chemical induced*: High dose steroids, vincristine, azathioprine, alpha-interferon, diazoxide, beta-blockers, thiazides, pentamidine, olanzapine 6. *Infections*: Congenital rubella, CMV and others 7. *Uncommon forms of immune mediated diabetes*: Stiff person syndrome, APS-1, IPEX syndrome, type B insulin resistance 8. *Miscellaneous genetic syndromes sometimes associated with diabetes*: Down, Turner, Prader-Willi and Laurence-Moon-Biedl syndromes, myotonic dystrophy, Friedreich ataxia
Gestational diabetes	

Abbreviations: DM, diabetes mellitus; MODY, maturity onset diabetes of the young; FCPD, fibrocalculous pancreatopathy; CMV, cytomegalovirus; APS, autoimmune polyglandular syndrome; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome.

Table 2 Distinction between type 1 and type 2 diabetes mellitus

Feature	T1DM	T2DM
Age at onset	Any age; the most common in pediatric age group	Adults and adolescents
Family history of DM	Uncommon (< 10%)	Common (> 75%)
Family history of autoimmune diseases	Common	Uncommon (coincidental)
Association with HLA DR3/DR4	Strong	Not associated
Duration of symptoms before diagnosis	Short (days or weeks)	Long (months to years)
Presentation with ketosis	Common	Rare
Weight at diagnosis	Lean	Obese
Acanthosis	Not a feature	Common
Hypertension	Not a feature	Not uncommon
Evidences of PCOD	Not a feature	Common
Pancreatic autoantibodies	Positive	Negative
C-peptide	Low	Normal or raised but low for the level of BG
Insulin requirement	Lifelong; essential for survival	Episodic, if at all

Abbreviations: PCOD, polycystic ovarian disease, DM, diabetes mellitus.

Other Specific Types of Diabetes

It is important to look beyond T1DM and T2DM in pediatric patients with DM with the clues highlighted in **Box 1**. Patients fulfilling any of these criteria may be categorized into an alternative diagnosis which includes the following entities:

Monogenic Defects in Beta Cell Function

This group results from mutations in a single gene affecting insulin production or release. A specific diagnosis can be made only by DNA testing. Disorders from this group that may be encountered by the pediatrician are maturity onset diabetes of the young (MODY), neonatal DM (transient or permanent), Wolfram syndrome and Roger syndrome. Other disorders in this group (mitochondrial DM, genetic defects in conversion of proinsulin to insulin and defects with production of a mutant insulin molecule) are rarely reported in childhood. Neonatal diabetes is discussed below. Six varieties of *MODY* each due to a single gene defect have been identified. The onset of DM is below age of 25 years, inheritance is autosomal dominant and three successive generations are afflicted; patients are not obese and do not have pancreatic autoantibodies. Three varieties are relatively common: these include mutations in glucokinase (GCK), hepatocyte nuclear factor (HNF)-1-alfa and HNF-4-alfa. The *Wolfram syndrome* of diabetes insipidus, DM, optic atrophy and sensorineural deafness is due to a mutation in the

WSF1 gene. DM in this condition presents at a mean age of 6 years and is insulin dependent from the outset. The *Roger's syndrome* refers to a condition with thiamine responsive megaloblastic anemia, deafness and DM showing partial response to thiamine but ultimately needing insulin. It is caused by a mutation in the *SLC19A2* gene.

Neonatal Diabetes

It refers to DM with onset below the age of 6 months. It may be transient or permanent. *Transient neonatal diabetes* is due to abnormalities of chromosome 6q24 with over expression of paternally expressed genes in 65% of cases. The condition is self-limited and resolves by 18 months, though 50–60% will have a recurrence of DM later in life. *Permanent neonatal diabetes* is a genetically heterogeneous disorder with derangement of beta cell function or reduction in pancreatic mass, with or without syndromic features. Mutations of the *KCNJ11* gene and the *ABCC8* gene which encode the two protein subunits (Kir6.2 and SUR1 respectively) of the ATP sensitive potassium channel in the beta cells account for nearly half the cases of permanent neonatal diabetes. Correct identification of these two entities is important as they can be managed with oral hypoglycemic agents (sulfonylureas).

Genetic Defects in Insulin Action

Included in this category are single gene mutations that cause resistance to the action of insulin either by affecting the insulin receptor or by affecting adipose tissue development or function. They have certain features in common: acanthosis nigricans, severe hyperinsulinemia and hyperandrogenism without obesity and with very high insulin requirements when DM sets in. These syndromes include the type A insulin resistance, and Rabson-Mendenhall syndromes and leprechaunism (Donohue syndrome). Disorders of adipose tissue (lipoatrophy syndromes) have severe insulin resistance due to a defect in post-receptor signal transduction pathways. Fat loss may be partial or total, congenital or acquired. Severe insulin resistance is treated with insulin sensitizers (metformin, glitazones), very high dose insulin (using U-500 insulin or insulin pump), recombinant insulin like growth factor-1 (IGF-1), or recombinant leptin.

Diseases of the Exocrine Pancreas

Loss of pancreatic tissue due to disease, surgical removal, toxic damage or radiation can result in DM. Since the alpha cells

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BOX 1 When to suspect that diabetes in a pediatric patient is not type 1

- Obese adolescent with acanthosis, hypertension and/or features of PCOD and a strong family history of T2DM.
- Onset of DM < 6 months of age.
- History of DM in a parent (autosomal dominant inheritance).
- History of recurrent abdominal pain/history suggestive of exocrine pancreatic insufficiency.
- Preceding chronic ailment in a patient diagnosed with DM.
- Patient on medications known to cause insulin deficiency or resistance.
- Patient with syndromic (dysmorphic) features or lipoatrophy.
- Deafness or optic atrophy in patient/family.
- Lean patient with very high insulin requirement (especially if associated acanthosis nigricans and hyperandrogenism).
- History/findings suggestive of endocrinopathies.
- Absence of pancreatic antibodies at outset.
- Very low insulin requirement with normal C-peptide after 2–3 years of DM.

Abbreviations: PCOD, polycystic ovary disease; DM, diabetes mellitus.

producing glucagon are also affected these patients are more prone to hypoglycemia. Possible causes include cystic fibrosis, fibrocalculous pancreatopathy (FCPD), chronic pancreatitis, traumatic pancreatic damage, alpha-1-antitrypsin deficiency (this enzyme prevents beta cell apoptosis), autoimmune pancreatitis, hereditary hemosiderosis, thalassemia major, pancreatectomy for persistent neonatal hyperinsulinemia and radiation exposure of the tail of the pancreas (where islet cells are concentrated). Besides features of the underlying cause, patients may have features of exocrine pancreatic insufficiency, recurrent abdominal pain and even pancreatic calcification.

Endocrinopathies

Primary oversecretion of growth hormone, cortisol, epinephrine, thyroid hormone and glucagon can cause diabetes especially in patients with underlying defects in insulin secretion. When the hormone excess state has been corrected, diabetes is usually reversed.

Drug or Chemical Induced Diabetes

It refers to new development of hyperglycemia that meets the definition of DM due to intake of a drug. Drugs used in oncology (L-asparaginase, high dose steroids, interferon alfa), transplantation medicine (calcineurin inhibitors including tacrolimus, sirolimus, cyclosporine A), neurosurgery (high dose steroids), psychiatry (clozapine, olanzapine, risperidone), HIV management (protease inhibitors), cardiac disorders (thiazides, beta blockers, statins, nicotinic acid) and anti-infective drugs (pentamidine, certain fluoroquinolones) can predispose to diabetes or can precipitate diabetes either by affecting insulin release or increasing insulin resistance. Diazoxide, a potassium-ATP channel opener, used in management of hypoglycemia due to hyperinsulinemia can lead to a transient DM.

Infections

Coxsackie virus B, cytomegalovirus, adenovirus, mumps, Epstein-Barr virus and rotavirus have all been implicated in causation of diabetes but without convincing evidence. Babies born with congenital rubella may develop autoimmune diabetes (besides autoimmune thyroid dysfunction) in the second decade of life or later.

Uncommon Forms of Immune Mediated Diabetes

Included in this category are: (1) The *stiff person syndrome:* a disorder with fluctuating rigidity and spasms involving axial muscles. It generally presents at 30–60 years of age but is occasionally reported in children below 3 years. It is associated with markedly raised GAD antibody and with the other autoimmune diseases. (2) *Type B insulin resistance syndrome:* caused by antibodies directed at the insulin receptor is seen in females over the age of 20 years and is associated with acanthosis nigricans, hyperinsulinemia, and other autoimmune disorders; 50–80% have

SLE. (3) *Monogenic syndromes with autoimmune diabetes*: included in this category is the IPEX syndrome (with immunodysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) characterized by male child with severe enteropathy, dermatitis, neonatal DM, autoimmune disorders involving thyroid, liver, RBC and platelets, markedly raised IgE and eosinophilia. This is caused by mutations in *FOX3* gene. Autoimmune polyglandular failure (APS-1) is another example.

Miscellaneous Genetic Syndromes Sometimes Associated with Diabetes

Diabetes mellitus occurs with higher frequency in certain syndromes. T1DM is four to six times more common in *Trisomy 21* than in general population and may be associated with AITD and CD. *Turner syndrome* is commonly associated with insulin resistance and T2DM rather than T1DM even though autoimmunity (particularly AITD and CD) is commonly associated. Children with *Prader Willi syndrome* should be screened for T2DM, the risk of which increases when on growth hormone therapy. Fifteen percent with *Laurence-Moon-Bardet-Biedl syndrome* will have symptomatic T2DM and a further 30% may be picked up on screening oral glucose tolerance test (OGTT). These patients may have polyuria and polydipsia also due to nephrogenic diabetes insipidus. Patients with *Alström syndrome* have insulin resistance with acanthosis nigricans and develop T2DM in early teens or in adult life. Patients with *Friedreich ataxia* may have acute presentation requiring insulin whereas patients with *myotonic dystrophy* are at high-risk of developing T2DM.

Gestational Diabetes Mellitus

Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy. It is diagnosed by a 75 g OGTT done at 24–28 weeks of gestation. The diagnostic levels of venous plasma glucose are more than or equal to 92 mg/dL (fasting), 180 mg/dL (1 hour) and 153 mg/dL (2 hours).

STAGING OF DIABETES MELLITUS

All types of DM pass through the stages of normoglycemia, impaired glucose regulation, and finally, frank DM **(Table 3)**. *Normoglycemia* is defined as fasting plasma glucose (FPG) less than 100 mg/dL and 2 hours postglucose (PG) value less than 140 mg/dL on standardized OGTT. *Impaired glucose regulation or categories of increased risk for DM are* prediabetic states. These include: (1) *impaired fasting glycemia* (IFG): defined as FPG between 100 mg/dL and 125 mg/dL and (2) *impaired glucose tolerance* (IGT): defined as 2 hours PG value between 140 mg/dL and 199 mg/dL.

In patients with classic symptoms of hyperglycemia a single random plasma glucose (done at any time of the day and at any time in relation to meals) of more than or equal to 200 mg/dL is sufficient to clinch the diagnosis. In asymptomatic patients, an OGTT (glucose dose of 1.75 g/kg to a maximum of 75 g) is needed

Table 3 Staging of diabetes and their diagnostic criteria

Stage	Fasting plasma glucose	2 hours postglucose plasma glucose	HbA$_{1C}$
Normoglycemia	< 100 mg/dL	< 140 mg/dL	< 5.7%
Impaired fasting glycemia (IFG)	100–125 mg/dL	< 140 mg/dL	5.7–6.4%
Impaired glucose tolerance (IGT)	< 100 mg/dL	140–199 mg/dL	5.7–6.4%
Diabetes (asymptomatic patient)	≥ 126 mg/dL*	≥ 200 mg/dL*	≥ 6.5%

N.B.: In a patient with classical symptoms of DM or hyperglycemic crises a single random plasma glucose ≥ 200 mg/dL suffices to confirm the diagnosis.
* Any one value being abnormal (on two separate occasions) is needed for diagnosis of DM.

for diagnosis. A FPG of more than or equal to 126 mg/dL *or* a 2 hours postglucose value more than or equal to 200 mg/dL on two different occasions is diagnostic.

Glycosylated hemoglobin (HbA_{1c}) of more than or equal to 6.5% is also laid down as diagnostic criteria for DM, with a value between 5.7 and 6.4% being indicative of increased risk of DM; however, there are problems with assay standardization and individual variations in relationship between blood glucose and HbA_{1c}.

MORE ON THIS TOPIC

Acerini C, Craig ME, de Beaufort C, et al. Introduction to ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes. 2014;15:1-3.

Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocrine Rev. 2008; 29: 265-91.

American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997; 20: 1183-97.

Atkinson MA, Eisenbarth GS, Michel AW. Type 1 diabetes. Lancet. 2014; 383: 69-82.

Canivell S, Gomis R. Diagnosis and classification of autoimmune diabetes mellitus. Autoimmun Rev. 2014;13:403-7.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33:676-82.

Stone MA, Camosso-Stefinovic J, Wilkinson J, et al. Incorrect and incomplete coding and classification of diabetes: a systematic review. Diabet Med. 2010;27:491-7.

IN A NUTSHELL

1. Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease occurring due to destruction of the pancreatic beta cells in the islets of Langerhans. Insulin is essential for survival in type 1 DM.
2. Patients with T1DM and their family members are more prone to other autoimmune diseases such as autoimmune thyroid disease, celiac disease, or pernicious anemia.
3. Type 2 DM is characterized by overt obesity or increased abdominal fat, hypertension, acanthosis, dyslipidemia and, in females, polycystic ovarian disease. This responds to oral hypoglycemic drugs.
4. The evolution of diabetes proceeds from impaired glucose tolerance or impaired fasting glucose to overt diabetes. However, in young children with Type 1 DM, the gap between impaired glucose tolerance and overt DM is very small.
5. Other uncommon types of DM in the pediatric age group include neonatal DM, other forms of monogenic diabetes, Wolfram syndrome, pancreatic diseases, syndromic conditions, monogenic disorders of insulin action, and drug induced diabetes.

Chapter 44.23
Type 1 Diabetes Mellitus
Aspi Irani

Diabetes mellitus (DM) is second only to asthma as the most common chronic disease of childhood and type 1 diabetes mellitus (T1DM) is by far the most common variety of DM in pediatric age group. There has been a 3.2% rise in cases each year since 1990; particularly in the 1–5 years age group. Early diagnosis can be lifesaving as late presentation after onset of diabetic ketoacidosis (DKA) carries a significant mortality. Appropriate treatment prevents or significantly delays the long-term complications associated with this disease. This is the only disease in which the patients play the key role in day to day management; hence, patients must receive intensive, ongoing education in diabetes self-management as well as regular counseling to help them to cope with the disease burden and ensure compliance.

EPIDEMIOLOGY

There is a marked geographic variation in incidence of T1DM, the lowest being in China, Pakistan, Thailand and Ethiopia (< 1/100,000/year) and the highest in Finland, Sweden and Sardinia (40/100,000/year). The Indian Council of Medical Research (ICMR) has started a registry for young diabetics in India. A study from Karnataka (2008) spanning 13 years reported an incidence of 3.7 (in boys) and 4.0 (in girls) per 100,000. A recent study from Haryana (2010) reported an overall prevalence of 10.2 per 100,000, with a sixfold higher prevalence in urban (26.6) as compared to rural (4.27) areas. India has a relatively low incidence rate but in view of the large population accounts for a very large absolute number of cases. There are about 1 lakh children in India with T1DM. It is estimated that one in every five children with T1DM worldwide is Indian. There is no sex difference in T1DM when onset is below age of 15 years; above 15 years males have a higher incidence. There is a seasonal variation in presentation with fewer cases presenting in summer months than in winter. The worldwide increase in incidence of T1DM particularly in younger age groups may partly be due to a left shift in age of onset rather than an absolute increase in lifetime risk of the disease. Reducing incidence of infections may be a factor leading to the higher incidence of autoimmune DM (*hygiene hypothesis*).

ETIOLOGY

Type 1 diabetes mellitus is the result of failure of insulin production from selective destruction of the beta cells due to autoimmunity (in 80–95%) or due to an unidentifiable mechanism. The damage is mediated by T-lymphocytes in patients with a genetic predisposition closely related to the human leukocyte antigen (HLA) class 11 genes involved in immune regulation. Only 5% of T1DM patients will lack HLA-DR3 and, HLA-DR4. Genetic markers conferring increased risk include HLA DR3/DQ2 or HLA DR4/DQ8. Some genetic factors exert a protective influence (HLA DR15/DQ6). Whereas 50% of genetic susceptibility is due to HLA variants; the remaining 50% comes from 40 other genes; the most common being the *INS* gene (encoding proinsulin) and the *PTPN22* gene (involved in T-cell regulation).

In the general population, the risk of developing T1DM is 0.3%, whereas in those with an affected random sibling or first degree relative it is 5%. The risk is 30–50% if a monozygotic twin is affected; 14% in case of an HLA identical sibling and 6–10% if a dizygotic twin is affected. The risk is 7% when the father is affected and 2% when the mother is affected.

Not all genetically predisposed persons will progress to clinical diabetes; thus environmental factors (nutritional or viral) appear to play a crucial role in initiating or facilitating autoimmunity. Vitamin D deficiency, nitrates in drinking water, early bovine milk protein exposure, early gluten exposure, omega-3 fatty acid deficiency and lack of breastfeeding are suspected to have a role in triggering T1DM. Viruses that may trigger beta cell autoimmunity include congenital rubella, enteroviruses, mumps, echovirus, Epstein-Barr virus (EBV), rotavirus and retroviruses.

Antibodies directed at antigens in the beta cell can be detected in serum, months to years before clinical diabetes. These include GAD antibodies, IAA, ICA, IA-2, and antibodies to ZnT8. These are not the cause of diabetes but are markers of the autoimmune process. There is a positive correlation between the number and titer of antibodies and the risk of progression to diabetes.

T1DM develops slowly over several months or years evolving through various stages **(Box 1)**. When a genetically predisposed child is exposed to certain environmental factors, autoimmunity to beta cells may be triggered, which can affect the functioning of the cells with initial reduction in first phase insulin release on intravenous glucose tolerance test (IV-GTT), followed by abnormal oral glucose tolerance test (OGTT) and finally clinical symptoms of DM.

PATHOPHYSIOLOGY

Insulin is an anabolic hormone; lack of insulin would therefore have catabolic effects in the body accentuated by the unopposed action of the stress hormones. This hormonal imbalance leads to reduced glucose uptake and utilization by muscle, adipose tissue and liver with increase in glycogenolysis and gluconeogenesis resulting in raised blood glucose. Proteolysis and lipolysis release amino acids and glycerol respectively which are diverted for gluconeogenesis adding to hyperglycemia.

Rising blood glucose leads to (1) osmotic diuresis with loss of fluid, electrolytes and minerals (particularly potassium and phosphate) in urine when blood glucose crosses the renal threshold; (2) increase in serum osmolality by 1 mOsm/L for each 18 mg/dL rise in blood glucose; (3) rise in glycosylated hemoglobin (HbA_{1c}) as glucose in circulation binds irreversibly to hemoglobin. The combined effect of dehydration, depletion of RBC 2,3-DPG (from phosphate loss in urine) and raised HbA_{1c} is to cause tissue hypoxia by reducing oxygen delivery and release to the tissues. Dehydration adds to hyperglycemia by restricting renal excretion of glucose. Hypophosphatemia causes insulin resistance and muscle weakness. Hypokalemia leads to ileus.

Proteolysis and lipolysis cause muscle wasting and loss of subcutaneous fat. Free fatty acids released from adipose tissue are taken up by the liver and esterified to triglycerides or oxidized to ketone bodies. The former are stored in the liver, resulting in fatty liver or released in the circulation causing hyperlipidemia.

BOX 1 **Steps in the evolution of Type 1 diabetes mellitus**

- Individual with genetic predisposition for T1DM→
- Exposure to environmental trigger/triggers→
- Onset of autoimmune attack directed at beta cells in pancreatic islets→
- Reduction in first phase insulin release on IV-GTT→
- OGTT becomes abnormal→
- Clinical symptoms of DM:
  - Stage of metabolic recovery→
  - Honeymoon phase→
  - Intensification phase→
  - Established diabetes.

Abbreviations: T1DM, type 1 diabetes mellitus; IV-GTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

Ketones are excreted in the urine bound to equimolar amounts of potassium and sodium causing further electrolyte depletion. Ketone bodies being acidic are neutralized by the buffer systems particularly bicarbonate; as bicarbonate level begins to drop compensatory mechanisms stimulate the respiratory center in an attempt to wash out carbon dioxide and maintain blood pH. Hyperventilation aggravates pulmonary water loss, adding to dehydration. When this compensation fails, metabolic acidosis rapidly sets in with its vasodilatory and negative ionotropic effects which may culminate in shock. The degree of stupor in DKA correlates best with serum osmolality.

CLINICAL FEATURES

The clinical presentation of T1DM is fairly typical **(Box 2)**. Early symptoms result from hyperglycemia; these include the classical triad of polyuria, polydipsia, polyphagia along with weight loss and weakness. Weight loss despite an increased food intake is an important clue. Secondary nocturnal enuresis or recent onset nocturia are other important pointers. Some patients may complain of pruritus or blurring of vision.

At a later stage, ketosis develops. There is anorexia, vomiting, abdominal pain and distension. There have been many instances of hasty surgery undertaken with a mistaken diagnosis of surgical acute abdomen. There is hepatomegaly due to fatty infiltration. The patient may have tachypnea with *air hunger* (Kussmaul respiration) due to metabolic acidosis and a peculiar *acetone odor* to the breath. Breathlessness without any findings in the respiratory or cardiovascular systems should raise the suspicion of DM with ketosis. There would be signs of dehydration, though these are partially masked as ECF volume is relatively well preserved. Polyuria in a dehydrated patient should make one suspect DM.

Untreated, the patient becomes progressively drowsy. Evidence of an associated infection should be sought out especially in patients with fever. Shock and coma can occur in untreated diabetes but are uncommon.

DIFFERENTIAL DIAGNOSIS

Diabetes mellitus needs to be differentiated from (1) *Other conditions causing polyuria and polydipsia* such as diabetes insipidus, renal tubular acidosis, psychogenic polydipsia and the *daytime urinary frequency syndrome*. In each of these conditions the blood glucose levels would be normal. In the day time urinary frequency syndrome the volume voided is small, there is no nocturia, nocturnal enuresis or polydipsia. (2) *Other conditions associated with glycosuria*: this includes renal glycosuria and Fanconi syndrome. (3) *Conditions associated with ketoacidosis and hyperglycemia*: there have been reports of certain inborn errors of metabolism (isovaleric acidemia, methylmalonic acidemia and propionic acidemia) and organophosphorus poisoning presenting as DKA. DKA should be considered in the differential diagnosis of a child presenting with acute abdomen, metabolic acidosis, or coma.

BOX 2 Clinical clues suggesting the diagnosis of diabetes mellitus in a child

- Classical triad of polyuria, polydipsia, polyphagia
- Weakness and weight loss despite increased food intake
- Recent onset nocturia or secondary enuresis
- Observation of ants collecting around urine
- Recurrent/persistent vaginal candidiasis
- Tachypnea with no findings in respiratory or cardiovascular systems and a peculiar breath odor
- Polyuria in a dehydrated child
- Differential diagnosis of acute abdomen
- Differential diagnosis of coma.

STAGES OF CLINICAL DIABETES

Childhood T1DM typically evolves through four stages **(Box 1)**. At the time of initiation of therapy (the stage of *metabolic recovery*) subcutaneous insulin requirement is fairly high on account of the accumulated metabolic deficit, the high levels of stress hormones and compensatory hyperphagia. Soon, there is a dramatic improvement in symptoms and a rapid weight gain. The liver may enlarge due to deposition of glycogen, peripheral edema may occur, transient cataracts are described, variations in visual acuity are common and some patients may complain of temporary hair loss. This initial stage is followed after the first few days or weeks by the *honeymoon or remission phase* when insulin requirement drops dramatically due to regression of the inflammatory changes in the islets allowing the remaining beta cells to function better. Insulin sensitivity also increases once hyperglycemia is controlled and levels of stress hormones decline. This stage may be heralded by recurrent episodes of hypoglycemia. A few children may actually be able to maintain reasonably good control without any insulin though it is advisable not to omit insulin altogether. After an average of 3–12 months, insulin requirement begins to rise again (the *intensification phase*), as beta cell destruction progresses relentlessly. Within 1–2 years after clinical onset of the disease, the patient enters the phase of *total diabetes* when endogenous insulin production is negligible and no longer plays a significant role in glucose homeostasis.

MANAGEMENT

Philosophy of Management

Prior to the discovery of insulin in the year 1921, T1DM was a fatal disease. With the availability of insulin T1DM can be controlled but a cure is still elusive. Further, the disease is associated with a significant short-term and long-term morbidity. This is because, in spite of major advances over the past 90 years, insulin replacement therapy is far from perfect. Exogenous insulin is delivered subcutaneously rather than in portal circulation, hence there are high levels in systemic circulation and low levels in liver. Insulin administration is not linked to prevailing blood glucose but is estimated based on anticipated eating and activity pattern. Exogenous insulins have a lag period and a long half-life hence once injected, course correction is not possible and there is minimum flexibility. The results of day to day management are largely dependent on the patient's compliance and motivation.

For the reasons mentioned above, it is unrealistic to expect a normal metabolic milieu at all times; thus certain arbitrary criteria have been laid down as the goals of management. These are: (1) child should be asymptomatic, with no polyuria, nocturia or weakness from hyperglycemia; no symptoms attributable to hypoglycemia and no episodes of DKA; (2) child should be attending school regularly, participating in all age appropriate activities, and leading a reasonably happy childhood; (3) child should be growing and maturing normally; (4) child and family should be emotionally stable and educated in diabetes self-management skills; (5) the glycosylated hemoglobin (HbA_{1c}) and a majority of the self-monitored blood glucose values should be within an arbitrarily defined target range; (6) child should remain free of the microvascular and macrovascular complications of diabetes.

The results of two landmark studies (The DCCT and the EDIC studies) form the basis of the philosophy of T1DM management. The DCCT showed that (1) intensified management [basal-bolus insulin regimens or insulin pump therapy with frequent self-blood glucose monitoring (SBGM) and 24 hours telephonic back up guidance] resulted in significantly lower HbA_{1c} as compared to conventional therapy. (2) Any sustained improvement in

HbA$_{1c}$ without significant swings in blood glucose, was associated with over 50% reduction in risk of development and progression of microvascular complications. (3) These benefits however came with threefold increased risk of hypoglycemia and twofold increased risk of obesity. *The EDIC study* which followed the DCCT showed that: (1) risk of macrovascular complications too was reduced with intensified management; (2) with availability of better insulins and monitoring methods over time, complications of intensified management reported in the DCCT were reduced; (3) It was difficult to obtain the same degree of control as in the DCCT without consistent 24 hours telephonic back up which was an important component of the DCCT; (4) The benefits of any past period of good control during the DCCT continued to accrue even if the same degree of control could not be maintained in the follow up EDIC study.

Thus one should aim to achieve as low a HbA$_{1c}$ as possible for the maximum possible period of time, with a low standard deviation and without risk of significant hypoglycemia.

The four components of management of T1DM are: (1) insulin therapy, (2) medical nutritional therapy, (3) planned physical activity and (4) therapeutic monitoring (at home and periodically at the diabetes center). Patient education and emotional stability constitute the foundation on which these four pillars of diabetes management rest. A team approach is mandatory for effective management; the team should comprise of a specialist in childhood diabetes, a pediatrician, a nutritionist, a clinical psychologist, a social worker, a nurse educator and some well-adjusted senior patients/their parents.

Insulin Therapy

Lifelong insulin therapy is essential for the survival of children with diabetes. Originally, insulins were derived from beef and pork pancreas and contained several impurities; later insulins were synthesized in the laboratory by recombinant DNA technology and are made identical in structure to human insulin besides being highly purified. These so-called *human insulins* were classified according to their time action curve as short acting (regular), intermediate acting (NPH and Lente) and long acting (Ultralente). Recently, Lente and Ultralente insulins have been discontinued and only regular and NPH insulins are available. A number of designer insulins or *insulin analogs* have been developed. These insulins are structurally modified with an aim to alter their time action profile. The analogs may be classified as rapid acting (Lispro, Aspart, and Glulisine), long acting (Detemir and Glargine) or ultra-long acting (Degludec) **(Table 1)**.

Table 1 Time action profile of available insulins (Figures shown here are approximate; these may vary from person to person depending on the site and depth of injection and other factors)

Insulin category	Insulin	Onset (hours)	Peak (hours)	Duration (hours)
Rapid acting analog	Lispro	0.25	1–3	3–5
	Aspart	0.25	1–3	3–5
	Glulisine	0.25	1–3	3–5
Short acting human insulin	Regular	0.5–1.0	2–4	6–8
Intermediate acting human insulin	NPH	1–3	4–8	12–16
Long acting analog	Glargine	2–3	None	16–24
	Detemir	2–3	3–9	6–23
Ultra long acting analog	Degludec	0.5–1.5	None	> 24

Which Insulin to Use?

In management of DKA either human regular insulin as an intravenous infusion or a rapid acting analog given subcutaneously every 1–3 hours is employed. Insulin pump therapy employs only rapid acting insulin analogs. For supplemental insulin doses on sick days; only regular insulin or preferably a rapid acting analog is used. In all other instances the patient is managed with a combination of rapid or short acting insulin plus NPH or long acting insulin.

Rapid acting insulin analogs have several advantages over human regular insulin. The onset of action is very quick, hence the child can eat soon after the injection; there is no need to wait 20–30 min as in the case of human regular insulin. In toddlers who cannot be relied on to eat after the insulin dose, analogs may be injected immediately after the meal. Analogs achieve a quicker and higher peak level and their action declines significantly within 3 hours making them better suited to control postmeal glycemia with less risk of hypoglycemia before the next meal or during the night hours; this factor also reduces the need for frequent snacking.

The long acting analogs have the advantage over NPH insulin in that they give a more steady blood level (unlike NPH which has a distinct peak) so that there is less need for snacking between meals and less risk of nocturnal hypoglycemia. They have very little day to day variability in absorption (for NPH insulin this is > 25%) thus the action is more predictable. Further Glargine insulin works for 24 hours in 80% of children hence a single injection a day suffices; with NPH and Detemir, two daily doses are needed.

Insulin Regimens

There are two types of insulin regimens: the split-mix regimen and the bolus-basal regimen **(Table 2)**. In the *split-mix regimen* the patient injects a mixture of short or rapid acting insulin and NPH insulin two times a day (before breakfast and before dinner). It works on the (unphysiological) principle of *one insulin for one time period* with the morning short acting covering the period from breakfast to lunch, the morning NPH working predominantly between lunch and dinner, the evening short acting covers the postdinner period till bedtime or beyond and the evening NPH works overnight till breakfast time. In the *basal-bolus regimen* an attempt is made to mimic the physiologic pattern of insulin release: one or two injections of a long acting insulin are given to provide basal insulin (that which regulates hepatic glucose release in the fasting state) while three to four injections of a short acting insulin or rapid acting analog are taken before major meals to control postmeal glycemia.

Insulin Dose

For day to day management the insulin dose depends on the stage of diabetes, the age of the patient and the pubertal stage. During the phase of metabolic recovery the insulin requirement is very high, in the range of 2–3 units/kg/day; this then drops to 0.5 units/kg/day or less in the honeymoon phase. When the patient reaches the stage of total diabetes the insulin requirement is 0.7–1.0 units/kg/day in prepubertal patients and 1.0–1.5 units/kg/day in pubertal patients. Insulin must be stored in the refrigerator, and should be injected subcutaneously with systematic site rotation (important to prevent lipohypertrophy).

Insulin Pump Therapy (Continuous Subcutaneous Insulin Infusion or CSII)

The insulin pump is a device, the size of a pager, which delivers insulin continuously in the subcutaneous space. It uses only a rapid acting insulin analog (the insulin with the shortest half-life) for bolus doses as well as for basal insulin. The basal infusion rate

Table 2 Commonly used insulin regimens

Regimen	Prebreakfast	Prelunch	Predinner	Bedtime
Split-mix regimen: 2 injections/day	Human regular or rapid acting analog + NPH		Human regular or rapid acting analog + NPH	
Split-mix regimen: 3 injections / day	Human regular or rapid acting analog + NPH		Human regular or rapid acting analog	NPH
Basal-bolus regimen with human insulins: 3 injections a day	Human regular + NPH	Human regular	Human regular + NPH	
Basal-bolus regimen with human insulins: 4 injections a day	Human regular + NPH	Human regular	Human regular	NPH
Basal-bolus regimen with insulin analogs	Rapid acting analog	Rapid acting analog	Rapid acting analog	Glargine*
Basal-bolus regimen with insulin analogs	Rapid acting analog + Detemir	Rapid acting analog	Rapid acting analog + Detemir	

*Glargine need not be given at bedtime; it can be given at any time of the day but the time should be fixed from day to day. Some may need two doses of Glargine in a day.

can be varied for different periods of the day (most patients require four basal rates), temporary basal rates can be set and it may be suspended for certain situations such as during unscheduled exercise. An appropriate basal rate is that with which blood glucose does not drop below normal during fasting. The bolus dose which is given before each major meal, can be calculated with reasonable degree of precision taking four factors in account: the carbohydrate content of the meal, the premeal blood glucose level, the activity planned (if any) after the meal, and the active insulin in the circulation. The grams of carbohydrates for which 1 unit of insulin is needed (carbohydrate: insulin ratio), is obtained by dividing a constant, i.e., 500 by the total daily insulin dose (TDD). The blood glucose in mg/dL expected to decline with 1 unit of rapid acting insulin (the so-called insulin sensitivity factor or ISF) is calculated by dividing a constant, i.e., 1800 by the TDD. Many pumps include a *bolus wizard* feature that calculates the bolus dose if the necessary data is fed in. The bolus can be delivered all at once (normal bolus) or staggered over 30 min to 4 hours (square wave bolus) or as a combination of the two depending on the type of food to be eaten: whether it has a high glycemic index (GI) carbohydrate or low GI with high fiber or fat content. The pump can be remote controlled, has a child lock and can be wirelessly connected to a Continuous Glucose Monitoring (CGM) device. CSII should be recommended for all motivated, intelligent and financially well off patients who are not adequately controlled on SC insulin regimens. Many centers have reported good results with use of CSII in the toddler age group.

Medical Nutritional Therapy
Children with diabetes need to grow normally hence calorie intake should be calculated using the same formula as for any normal child of the same age and sex. The entire family would benefit by eating the same meals as the child with diabetes and this would also ensure willing compliance on the part of the child. A special diet is needed only if the child is overweight or has celiac disease, hypertension or nephropathy.

Healthy Eating
The stress should be on eating foods that do not cause a rapid rise in blood glucose and avoiding items that can increase the risk of microvascular and macrovascular complications or renal damage. This implies eating three main meals and two to three mid-meal snacks to avoid swings in blood glucose; having 55–60% of the calories as carbohydrates, 30% as fat and 10–15% as proteins; eating meals with low GI and high fiber content (20 g per 1000 calories) if over 5 years of age; having salt in moderation (2 g/1000 calories), avoiding trans fats completely, restricting saturated fats and polyunsaturated fats to less than 10% of calories each and cholesterol to < 10 g/1000 calories; and preferring monounsaturated fats (10–15% of calories). Small amounts of sucrose, not exceeding 5% of total carbohydrate calories per day, may be permitted provided it is spaced out and taken as part of meals.

Vitamin and mineral supplements are not necessary. Non-caloric sweeteners (aspartame, saccharin, stevia, sucralose, acesulfame-K) are considered safe in small amounts. For a detailed description of meal planning, diet exchange lists and modifications to prevent exercise related hypoglycemia, the reader is referred to specialized texts.

Planned Physical Activity
Regular exercise is beneficial for various reasons: it gives the child a psychological boost and a sense of well-being, helps in weight control, increases insulin sensitivity and thereby lowers insulin requirement, lowers LDL cholesterol, helps in improving cardiac and lung function and leads to improved circulation in the limbs. Exercise in a child with adequately controlled DM can lead to hypoglycemia including delayed postexercise hypoglycemia for up to 16 hours after the activity. In a poorly controlled child, it can lead to worsening of control and ketoacidosis. Hence the need for *planned exercise* anticipating these problems and taking measures to prevent them **(Box 3)**.

Therapeutic Monitoring

Monitoring at Home
Self-blood glucose monitoring (SBGM) is the basis for fine tuning of therapy. The availability of point-of-care meters with lancets that allow for painless blood-letting has made this possible and revolutionized the management of T1DM **(Table 3)**.

BOX 3 Prevention of exercise related hypoglycemia

If activity is anticipated:
- Avoid injection in exercising limb.
- Reduce dose of insulin covering the exercise and postexercise period.
- Fine tune this adjustment with help of SBGM.

If activity is unanticipated:
- Have an additional snack prior to activity.
- Check bedtime and 3 am blood glucose for delayed post-exercise hypoglycemia.
- Have additional bedtime snack if blood glucose is low or in the lower range.

Abbreviation: SBGM, self-blood glucose monitoring.

Table 3 Suggested scheme for self-blood glucose monitoring (SBGM) over 7 days to obtain minimum meaningful data for pattern adjustment of insulin dose

Patients on basal-bolus regimens

	3 am	Prebreakfast	Postbreakfast	Prelunch	Postlunch	Predinner	Bedtime	Comments*
Monday		X		X		X		
Tuesday					X	X	X	
Wednesday	X	X		X				
Thursday			X		X		X	
Friday	X	X				X		
Saturday			X		X		X	
Sunday			X	X				

Patients on split mix regimen

	3 am	Prebreakfast	Prelunch	Predinner	Bedtime	Comments*
Monday			X		X	
Tuesday		X		X		
Wednesday	X	X				
Thursday				X	X	
Friday	X	X				
Saturday			X	X		
Sunday			X		X	

N.B.: Patients on basal-bolus regimens should perform three blood glucose tests a day, those on split-mix regimen need to do two tests a day. For interpretation of data it is important to have three or more values for each time period in 7 days (two values at 3 am would suffice). The pattern suggested here can be altered to suit patient's convenience.

*In the *comments* column, the patient mentions if any aberration in diet, activity or stress level may have been responsible for blood glucose values outside target range.

Urine ketones must be checked on days when the child is sick and therefore prone to ketoacidosis. It may also be useful in picking up undetected nocturnal hypoglycemia if tested in the fasting urine sample. A meter for home blood ketone estimation is available; this gives more reliable information than the urine ketone test (since it measures β-hydroxybutyrate whereas the urine test estimates acetoacetate). The target blood glucose would vary depending on age, time of the day and proneness to hypoglycemia **(Table 4)**. Patients on basal-bolus regimens and CSII can be taught to take corrective insulin supplements when their blood glucose is above the target range; this is calculated by dividing a constant (1800) by the total daily dose (TDD); the resultant value represents the anticipated drop in blood glucose in mg/dL with 1 unit of supplemental rapid acting insulin.

Continuous Glucose Monitoring Systems (CGMS)

A tiny flexible electrode (the glucose sensor) is inserted in the subcutaneous space to measure the interstitial glucose level every 5 min for 3–7 days. There are two types of continuous glucose monitoring systems: *historical* and *real time*. The former does not give real time values but the data can be downloaded at the end of the testing period on to a computer and analyzed. The latter transmits each reading to a monitor (usually the insulin pump) where it is displayed along with a graphical indicator of the glucose trend (speed and direction of blood glucose movement), allowing for earlier anticipatory intervention. A device that can switch off basal insulin delivery from the pump in anticipation of impending hypoglycemia is also being studied.

Monitoring at the Diabetes Center

The patient must be assessed at the diabetes center once in 3–6 months. During clinic visits the patient must be evaluated for adequacy of blood glucose control, growth and development, knowledge regarding diabetes self-management, emotional well-being, co-morbidities and complications screen. **Table 5** highlights the protocol for periodic laboratory tests in a patient with T1DM.

Diabetes Management in School

School authorities must know that the child has diabetes. They must be informed that she/he should be allowed to eat on time and to have a snack before the physical activity class and that he should be allowed to do all this in an unobtrusive manner. The school staff must be familiar with the early symptoms and signs of hypoglycemia and its first aid management. They should be informed that diabetes will not affect the child's academic abilities or her/his ability to participate in extracurricular activities; swimming however should be undertaken only under close supervision.

Patient Education (Box 4)

Patients with T1DM and their family members must be well versed with: (1) certain procedures: mixing and injecting insulin, injection site rotation, painless bloodletting, correct technique of measuring blood glucose, urine testing for ketones, blood testing

Table 4 Target HbA$_{1c}$ and blood glucose for different age groups in pediatric patients (as per recommendations of the American Diabetes Association 2014)

Age group	Target HbA$_{1c}$	Bedtime and 3 am blood glucose	Premeal blood glucose
< 6 years	< 8.5%	110–200 mg/dL	100–180 mg/dL
6–12 years	< 8.0%	100–180 mg/dL	90–180 mg/dL
13–18 years	< 7.5%	90–150 mg/dL	90–130 mg/dL

Table 5 Protocol for laboratory investigations in a pediatric patient with Type 1 diabetes mellitus (baseline and follow-up)

Frequency of testing	Investigations
Initially at onset of DM (but after recovery from ketosis and stabilization of blood glucose)	CBC with indices C-peptide Pancreatic antibodies (GAD, ICA, IAA, IA-2), Antithyroid antibodies and TSH Serum IgA and tissue transglutaminase IgA antibody Serum Lipids Urine for microalbumin 21-hydroxylase antibody Ophthalmic check-up including funduscopy
Once every 3 months	HbA$_{1c}$ (in a patient with hemoglobinopathy, fructosamine test* would be more reliable)
Once a year	CBC with indices TSH and antithyroid antibodies Tissue transglutaminase IgA antibody
Once a year after 2 years of onset of T1DM (if pubertal) or after 5 years (if prepubertal)	Urine for microalbuminuria Funduscopy Serum lipids (if baseline values were abnormal)

*Fructosamine test reflects average blood glucose over preceding 2–3 weeks.
Abbreviations: DM, diabetes mellitus; CBC, complete blood count; TSH, thyroid-stimulating hormone; T1DM, type 1 diabetes mellitus; GAD, glutamic acid decarboxylase; ICA, islet cell antibody; IAA, insulin autoantibody; IA2, insulinoma associated antigen 2.

BOX 4 Patient education

Basics: What is diabetes, what causes diabetes, what are the adverse effects of raised blood glucose and of ketones on the body?

Procedures: Mixing and injecting insulins, systematic site rotation, storing insulin; bloodletting for SBGM, checking blood glucose, urine ketone testing, blood ketone testing, and injecting glucagon.

Meal planning: Concept of healthy eating, use of diet exchange list, carbohydrate counting, eating on *sick days*; role of diet in preventing exercise related and sleep hypoglycemia.

Decision making: Recording SBGM results, target blood glucose, knowledge of which insulin controls which blood glucose and pattern adjustment algorithms. Corrective insulin supplements and insulin sensitivity factor.

Diabetes related emergencies: Prevention, early recognition and first aid management of hypoglycemia and ketoacidosis (including *sick day* management).

Living with diabetes: Dealing with stress; revealing diabetes state to peers/others; precautions in school; travelling with diabetes; marriage and career counseling; need to screen for complications, their prevention/early detection for timely corrective action; sex education and contraception; future hopes.

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for ketones and technique for mixing and injecting glucagon; (2) Principles of meal planning: what constitutes healthy eating, use of diet exchange lists, carbohydrate counting and use of insulin: carbohydrate ratio; (3) Recording and analyzing SBGM records: when and how frequently to check blood glucose and urine ketones, recording the results, the concept of target blood glucose, the principles of pattern adjustment and calculation of corrective insulin supplements. (4) Prevention, early recognition and first aid management of hypoglycemia and sick day management to prevent ketoacidosis.

Education has to be tailored to the patients' needs, their degree of motivation, intellectual abilities and financial status. Education has to be ongoing and is best done in groups of likeminded patients. Residential camps and one day camps provide an excellent medium for education coupled with informal psychotherapy and counseling.

Psychosocial Aspects

At the outset patients and their family members experience typical set of emotional reactions. There is an initial period of shock followed by denial. When the diagnosis is finally accepted, there is grief that a hitherto normal and healthy child will now have to spend a lifetime on injections and multiple restrictions. There is anger (the *why me?* feeling), false hopes (finding a cure or an alternative to insulin injections), anxiety (how will we manage everything?), worries about the future (will the child be able to lead a normal life?) and financial worries. Counseling, not only by the medical team but also by other well-adjusted patients can go a long way in helping them accept the diagnosis and treatment and to move ahead in life.

PREVENTION

The first step in preventing T1DM would be to identify those who are susceptible. Further, at the time of onset of T1DM, 10–20% of beta cells are still functioning; if these can be successfully preserved then control of DM would be smoother. Thus, attempts are being made to prevent T1DM at three levels.

Primary prevention This is for genetically predisposed individuals without evidence of pancreatic autoimmunity, by targeting presumed environmental triggers (avoidance of bovine milk protein in early life, vitamin D supplementation, supplementation with omega-3 fatty acids and delayed introduction of gluten).

Secondary prevention In those with evidence of pancreatic autoimmunity, immunomodulation/immunovaccination with oral and intranasal insulins is being tried. Earlier studies using nicotinamide and parenteral insulin showed no benefit.

Tertiary prevention During the honeymoon phase attempts are made to preserve remaining beta cell function. Studies completed so far, without success, have evaluated cyclosporine, prednisolone and azathioprine, parenteral insulin, nicotinamide and BCG vaccination. Newer trials using agents that may produce immunotolerance to beta cell antigens (anti-GAD vaccine, heat shock protein derived DiaPep277); or that block the beta cell specific immune attack (humanized anti-CD3 monoclonal antibodies: teplizumab, otelixizumab, anti-CD20 antibodies: rituximab, CTLA-4 antibodies, thymoglobulin, anakinra: an IL-1 receptor antagonist); or that enhance beta cell proliferation and inhibit apoptosis (incretins, alpha-1-antitrypsin) are underway.

RECENT ADVANCES

Type 1 diabetes mellitus at present is not a curable disease. Scientists are working on various approaches to relieve patients of the need to inject insulin and check blood glucose. These approaches include:

(1) *Development of a closed loop insulin pump*: with a microprocessor interposed between the CGM system and the CSII device to calculate and direct the release of appropriate amounts of insulin based on ambient blood glucose. (2) *Pancreas and kidney transplant*: in a patient with renal failure needing a kidney transplant for survival, a simultaneous pancreas transplant has been successfully employed with good results; this category of patients would need immunosuppression for the kidney transplant in any case. The surgical procedure carries significant risk. (3) *Islet cell transplants*: this is a simple procedure and can be done under local anesthesia; the chief problems have been in obtaining a sufficient number of islets as the only source is cadaveric donors; and the risks associated with a lifetime on immunosuppressants to prevent rejection of the islets. Work is also ongoing to find safer immunosuppressants for long term use. (4) *Genetic engineering*: cells have been created that can produce insulin but the difficulty lies in regulating their output of insulin in response to blood glucose concentrations. (5) *Stem cell transplants*: this could solve the problem of obtaining sufficient islets. Stem cells may be embryonic or pluripotent adult stem cells; they can be directed to produce insulin. The issues being studied and debated are: regulating insulin output, controlling the growth of the stem cells and preventing their rejection by the immune system. (6) *Inhaled insulins, insulin pills, skin patches* for transdermal insulin delivery and a *smart insulin* (insulin attached to a biodegradable polymer that releases the insulin in proportion to prevailing blood glucose) are all being studied.

IN A NUTSHELL

1. Diabetes mellitus is a common chronic disease of childhood.
2. Presentation with ketoacidosis is serious, and early diagnosis, aided by a high index of suspicion, can be lifesaving.
3. Intensive home blood glucose testing and diabetes management, resulting in excellent metabolic control, has been shown to delay or decrease the prevalence of long-term microvascular and macrovascular complications. Hypoglycemia is a limiting factor.
4. Diabetes education is the cornerstone of management as the patient and family plays a crucial role in day to day care.

MORE ON THIS TOPIC

Acerini C, Craig ME, de Beaufort C, et al. Introduction to ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes. 2014;15:1-3.

American Diabetes Association. Clinical practice guidelines 2014. Diab Care. 2014;37:S14-85.

Melendez-Ramirez LY, Richards RJ, Cefalu WT. Complications of Type 1 Diabetes. Endocrinol Metab Clin N Am. 2010;39:625-40.

The Diabetes Control and Complications Trial research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-86.

van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. Physiol Rev. 2011;91:79-118.

Chapter 44.24
Acute and Chronic Complications of Diabetes Mellitus

KG Ravikumar

Diabetes mellitus causes several short-term and long-term complications leading to increased morbidity and mortality. In the pediatric age group, acute complications such as diabetic ketoacidosis and hypoglycemia are more commonly seen. However, it is equally important to prevent chronic complications, which adversely affect the quality of life during adulthood. Chronic complications can be classified as either microvascular (e.g., retinopathy, nephropathy and neuropathy) or macrovascular (e.g., cardiovascular disease, cerebrovascular accidents and peripheral vascular disease). The list of acute and chronic complications in diabetes is given in **Box 1**. The Diabetes Control and Complications Trial (DCCT), which was a multicenter randomized controlled clinical trial, clearly indicated that intensive diabetic treatment reduces long-term complications.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter-regulatory hormones: catecholamines, glucagon, cortisol and growth hormone. DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments. The biochemical criteria for the diagnosis of DKA are:
- Hyperglycemia with a blood glucose more than 200 mg/dL
- Venous pH less than 7.3 or bicarbonate less than 15 mmol/L
- Ketonemia and ketonuria.

Clinical Features

Clinical manifestations of diabetic ketoacidosis are variable and include dehydration, rapid, deep, sighing (Kussmaul) respiration, nausea, vomiting and abdominal pain mimicking an acute abdomen and progressive obtundation and loss of consciousness.

BOX 1 Acute and chronic complications of diabetes

Acute
- Diabetic ketoacidosis
- Cerebral edema
- Other CNS complications
- Acute renal failure
- Hypokalemia and Hyperkalemia
- Hyperglycemic hyperosmolar state (HHS)
- Hypoglycemia

Chronic
- Microvascular complications
  - Nephropathy, Retinopathy, Neuropathy
- Macrovascular complications
  - Myocardial infarction, stroke
- Impaired growth and development
- Predisposition to other autoimmune conditions
- Predisposition to hypertension, dyslipidemia, obesity
- *Skin and joint complications*: Edema, necrobiosis lipoidica diabeticorum, limited joint mobility
- Lipodystrophy
- *Psychological issues*: Mental health and behavioral problems.

Fever may be present when there is associated infection. Investigations often show increased leukocyte count with left shift and nonspecific elevation of serum amylase. The severity of DKA is categorized by the degree of acidosis and is listed in **Table 1**.

Diabetic ketoacidosis can be differentiated from the other rarer diabetic emergency known as hyperglycemic hyperosmolar state (HHS) by the presence of plasma glucose concentration of more than 600 mg/dL with an arterial pH more than 7.30 and serum bicarbonate more than 15 mmol/L. HHS may also have mild ketonuria, absent to mild ketonemia and effective serum osmolality more than 320 mOsm/kg in the presence of stupor or coma.

Management of Diabetic Ketoacidosis

Emergency Assessment
Initial clinical evaluation in the emergency room is mandatory to confirm the diagnosis and determine its cause. The clinician should then assess the clinical severity of dehydration. At least 5% dehydration is present when there are clinical signs such as prolonged capillary refill time, abnormal skin turgor and hyperpnea. The child may have more than 10% dehydration if there are weak or impalpable peripheral pulses, hypotension and oliguria. The level of consciousness should be assessed at the time of admission.

Biochemical Assessment
Initial investigations should include plasma glucose, electrolytes, urea, creatinine, osmolality, venous (or arterial in critically ill patient) pH, PCO_2, calcium, phosphorus and magnesium concentrations, HbA_{1c}, hemoglobin and hematocrit or complete blood count. Urinalysis for ketones and glucose should be done. Culture of blood, urine and throat would be useful if there is evidence of infection.

Supportive Measures
Children with DKA often have altered consciousness and it is important to ensure the airway is secured. Continuous nasogastric suction is also required to prevent pulmonary aspiration in these cases. Two peripheral intravenous (IV) catheters should be inserted for insulin infusion and IV fluids. Arterial catheter is useful for monitoring of invasive blood pressure and for frequent sampling. Child should be connected to cardiac monitor for continuous electrocardiographic monitoring to assess T-waves. Oxygen is required for patients with severe circulatory impairment or shock. Antibiotics should be given to febrile patients after obtaining appropriate cultures of body fluids. Children who are unconscious need bladder catheterization to monitor urine output. Subsequent clinical and biochemical monitoring is done as listed in **Table 2**.

Principles of Water and Salt Replacement
Despite much effort to identify the cause of cerebral edema, an important complication seen in children during treatment of DKA, its pathogenesis is incompletely understood but the majority of authorities advocate slow rehydration to avoid cerebral edema. The Milwaukee protocol, which has been widely used, suggests correcting fluid deficit over a 24-hour period and switching over to low sodium containing fluids after the initial 2 hours of resuscitation. However, more recent recommendations from

Table 1 Severity of diabetic ketoacidosis

Category	Venous pH	Bicarbonate in mmol/L
Mild	Less than 7.3	Less than 15
Moderate	Less than 7.2	Less than 10
Severe	Less than 7.1	Less than 5

Table 2 Clinical and biochemical monitoring in diabetic ketoacidosis

Parameter	Frequency of monitoring
Vital signs (heart rate, respiratory rate, blood pressure)	Hourly
Neurological observations (Glasgow coma score) for warning signs and symptoms of cerebral edema	Hourly
Fluid input and output	Hourly
Capillary blood glucose	Hourly
Laboratory tests: Serum electrolytes, glucose, urea, calcium, magnesium, phosphorus, hematocrit, and blood gases	2 hourly for the first 12 hours and then as required
Urine ketones	6 hourly

British Society for Pediatric Diabetes (BSPED) and International Society for Pediatric and Adolescent Diabetes (ISPAD) suggest slower correction to reduce the incidence of cerebral edema. The differences between various DKA management protocols are listed in **Table 3**.

Initial fluids For children with DKA who presents in shock, it is recommended that circulatory volume is rapidly restored with isotonic saline (or Ringer's lactate) in 20 mL/kg boluses infused as quickly as possible.

Subsequent fluid management Use 0.9% saline for at least 4–6 hours, preferably up to 12 hours. Thereafter, the replacement should be with 0.45% saline with potassium chloride. Urinary losses should not routinely be added to the calculation of replacement fluid.

Fluid calculations The required amount of fluid given in DKA is calculated according to the formulae in **Table 4**. The total fluid requirement is calculated by adding maintenance fluid and deficit after deducting the fluids that have already been given. The hourly rate is calculated by dividing the total requirement by 48 in order to correct the fluid deficit over 48 hours.

Corrected sodium levels can be calculated according to the formula given in **Table 4**. Corrected sodium levels should rise as blood glucose levels fall during treatment. If they do not, then continue with normal saline and do not change to 0.45% saline. Once the blood glucose has fallen to 250 mg/dL or if the glucose fall is more than 90 mg/dL, add glucose to the fluid.

Insulin Therapy

Insulin should be started 1 hour after starting fluid replacement. The initial dose of insulin is 0.1 unit/kg/hour. This can be prepared by diluting 50 units of regular (soluble) insulin in 50 mL of normal saline to make the final solution of 1 unit in 1 mL. An IV bolus is unnecessary, and may increase the risk of cerebral edema. The dose of insulin should usually remain at 0.1 unit/kg/hour at least until resolution of DKA (pH > 7.30, bicarbonate > 15 mmol/L).

Potassium Replacement

Children with DKA suffer total body potassium deficits of the order of 3–6 mmol/kg. The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias. Therefore, replacement therapy is required regardless of the serum potassium concentration. If the patient is hypokalemic, start potassium replacement *at the time of* initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. The starting potassium concentration in the infusate should be 40 mmol/L. Potassium replacement should be continued throughout the IV fluid therapy and may be needed thereafter in the form of oral potassium chloride.

Acidosis

Severe acidosis is reversible by fluid and insulin replacement. Bicarbonate infusion is not required except in severe acidemia (arterial pH < 6.9) and in life-threatening hyperkalemia.

Table 4 Calculations used in management of DKA

Calculation	Formula
Fluid requirement	Maintenance + deficit − fluid already given
Maintenance fluid requirement	≤ 10 kg : 100 mL/kg/24 hour 11–20 kg: 1000 mL + 50 mL/kg/24 hour for each kg from 11–20 > 20 kg: 1500 mL + 20 mL/kg/24 hour for each kg >20
Deficit (liters)	% of dehydration × body weight (kg)
Hourly rate	(48 hours maintenance + deficit − resuscitation fluid already given) divided by 48
Anion gap	$Na − (Cl + HCO_3)$ Normal is 12 ± 2 (mmol/L) In DKA the anion gap is typically 20–30 mmol/L; an anion gap > 35 mmol/L suggests concomitant lactic acidosis
Corrected sodium	Measured Na + 2 ([plasma glucose −5.6]/5.6) (mmol/L)
Effective osmolality (mOsm/kg)	2 × (Na + K) + glucose (mmol/L)

Table 3 Comparison of various management protocols for diabetic ketoacidosis

	Milwaukee	BSPED	ISPAD
Revised in	1988	2004 and 2007	2009 and 2014
Initial bolus	10–20 mL/kg	10 mL/kg	20 mL/kg for shock, 10 mL/kg with hypotension
Insulin	0.05–0.1	0.1 (Never use 0.05)	0.1
Corrected over	23 hours	48 hours	48 hours
Fluid and insulin	Start together	Start insulin 1 hour after fluids	Start insulin 1–2 hours after start of fluids
Lowering of insulin infusion	Once hyperglycemia resolves	If pH > 7.3, glucose < 250 and when glucose containing fluid started	When resolution of DKA occurs (pH > 7.30, bicarbonate > 15 mmol/L)
0.9% NS	1 hour	At least 12 hours	At least 4 hours preferably 12 hours

Abbreviations: BSPED, British Society for Pediatric Diabetes; ISPAD, International Society for Pediatric and Adolescent Diabetes.

Transition to Subcutaneous (SC) Insulin

Oral fluids should be introduced when clinical status has improved and acidosis corrected. When oral fluid is tolerated, IV fluid should be reduced. When ketoacidosis has resolved, the child can be started on SC insulin. The first SC injection should be given 15–30 min (with rapid acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.

Complications during Treatment of Diabetic Ketoacidosis

The mortality rate from DKA in children is 0.15–0.30%. Cerebral edema accounts for 60–90% of all DKA deaths. Other rare complications include hypokalemia, hyperkalemia, severe hypophosphatemia, hypoglycemia, central nervous system complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis), peripheral venous thrombosis, sepsis, rhinocerebral or pulmonary mucormycosis, aspiration pneumonia, pulmonary edema, adult respiratory distress syndrome (ARDS), pneumothorax, pneumomediastinum and subcutaneous emphysema, rhabdomyolysis, acute renal failure and acute pancreatitis.

Cerebral Edema

The incidence varies from 0.5% to 6% in different countries with mortality up to 25%. Potential risk factors for cerebral edema are presence of severe hypocapnia at presentation after adjusting for degree of acidosis, increased blood urea at presentation, severe acidosis at presentation, bicarbonate treatment for correction of acidosis, an attenuated rise in measured serum sodium concentrations during therapy, high volumes of fluid given in the first 4 hours and administration of insulin in the first 1 hour of fluid treatment.

Warning signs and symptoms of cerebral edema include headache and slowing of heart rate, change in neurological status (restlessness, irritability, increased drowsiness, incontinence), specific neurological signs (e.g., cranial nerve palsies), rising blood pressure and decreased O_2 saturation. Clinical diagnosis is made based on the criteria mentioned in **Table 5**. One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4% **(Table 5)**.

Treatment of cerebral edema Treatment should be initiated as soon as the condition is suspected. Elevate the head of the bed. Reduce the rate of fluid administration by one-third. Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 min to 2 hours. Hypertonic saline (3%), 5–10 mL/kg over 30 min,

Table 5 Diagnosis of cerebral edema

Diagnostic criteria	• Abnormal motor or verbal response to pain • Decorticate or decerebrate posture • Cranial nerve palsy (especially III, IV and VI) • Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
Major criteria	• Altered mentation/fluctuating level of consciousness • Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state • Age-inappropriate incontinence
Minor criteria	• Vomiting • Headache • Lethargy or not easily arousable • Diastolic blood pressure > 90 mm Hg • Age < 5 years

BOX 2 Signs and symptoms of hypoglycemia
- Autonomic symptoms
  - Trembling, palpitations, cold sweatiness and pallor
- Neuroglycopenic symptoms
  - Difficulty in concentrating, slurred speech, poor judgment, confusion, memory defect, dizziness, unsteady gait, loss of consciousness and seizures
- Behavioral symptoms
  - Irritability, nightmares, inconsolable crying and erratic behavior
- Nonspecific symptoms
  - Hunger, headache, nausea and tiredness.

may be an alternative to mannitol or a second line of therapy if there is no initial response to mannitol. Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a $PCO_2 < 22$ mm Hg) is not recommended.

HYPOGLYCEMIA IN CHILDREN WITH DIABETES

Hypoglycemia is the most common complication during treatment of type 1 diabetes. In children with insulin-treated diabetes, hypoglycemia is defined as a glucose level of 70 mg/dL or less. The signs and symptoms of hypoglycemia are listed in **Box 2**.

As children and parents have difficulty recognizing early warning symptoms of hypoglycemia, frequent blood glucose monitoring should be encouraged. The term *hypoglycemia unawareness* is used when neuroglycopenic symptoms occur before autonomic activation, resulting in reduced awareness of onset of hypoglycemia. This is associated with decreased glucagon and epinephrine output and can be reversed by avoiding hypoglycemia for 2–3 weeks.

Diagnosis and Management

In *mild hypoglycemia*, the child or parent is able to recognize the symptoms and treat themselves. In children, 0.3 g/kg of glucose or equivalent carbohydrate raises blood glucose by 50 mg/dL. Sucrose or fructose containing juices can be used but milk and chocolate can delay the absorption of glucose due to their fat content. The goal of treatment is to restore blood glucose to 100 mg/dL. It is important to retest blood glucose after 10–15 min. After this, the next meal or snacks can be ingested.

In *severe hypoglycemia*, the child is unconscious and needs parenteral therapy with glucose or glucagon. Urgent treatment is required in all these cases and the best method is to administer IV/IM/SC glucagon at a dose of 10–30 µg/kg body weight. If glucagon is unavailable, intravenous dextrose can be used at a dose of 200–500 mg/kg given slowly. A dextrose concentration of 50% and above or rapid administration should be avoided. Buccal administration of glucose gel or honey is also a common practice, although there is no clear evidence of its efficacy. After the initial bolus of dextrose a slow intravenous infusion of 10% dextrose at a rate of 2–5 mg/kg/min may be required.

CHRONIC COMPLICATIONS OF DIABETES

Impaired Growth and Pubertal Development

Monitoring of growth and physical development and the use of growth charts is an essential part of management of children with diabetes. Poorly controlled diabetes can result in poor weight and height gain but it may also be contributed by other associated conditions such as celiac disease. In children with persistently poorly controlled diabetes hepatomegaly and late pubertal development can coexist with poor weight and height and a thick waxy skin and this is referred to as *Mauriac syndrome.* On the other hand, better diabetic control may result in excessive

weight gain partly contributed by excessive insulin administration. This is more likely to be seen during and after puberty. In such children, prevention of complications like polycystic ovary disease, hypertension, dyslipidemia and hyperandrogenism should be emphasized.

Associated Autoimmune Conditions

Children with type 1 diabetes have higher risk of developing other autoimmune conditions such as hypothyroidism, hyperthyroidism, celiac disease, vitiligo, Addison disease and the rare immunodysregulation polyendocrinopathy X-linked (IPEX) syndrome. Screening of thyroid function by testing for thyroid stimulating hormone and thyroid antibodies is recommended at the diagnosis of diabetes and every second year thereafter. Screening for celiac disease should be carried out at the time of diagnosis, annually for the first 5 years and every second year thereafter.

Skin and Joint Complications

Lipodystrophy, a term that includes *lipoatrophy and lipohypertrophy* is a known complication of use of insulin. Lipoatrophy is seen infrequently with human insulin but lipohypertrophy is seen in 48% of those with type 1 diabetes. Insulin absorption can be erratic and unpredictable and rotation of injections site should be advised to avoid this.

Necrobiosis lipoidica diabeticorum is well circumscribed, raised red lesions seen in pretibial region that may progress to ulcer formation. *Limited joint mobility (LJM)* is a bilateral painless contracture of finger joints and large joints with tight waxy skin. On examination, child has difficulty in approximating the palmar surfaces of interphalangeal joints.

Generalized *edema* due to water retention is a rare complication of insulin treatment. The edema spontaneously resolves with good glycemic control.

Microvascular Complications

Nephropathy

Nephropathy is a major cause of morbidity and mortality in type 1 diabetes mellitus. Diabetic nephropathy is defined as persistent proteinuria more than 500 mg/24 hour or albuminuria more than 300 mg/24 hour. Decreased glomerular filtration rate and hypertension are often present. The first clinical sign of incipient nephropathy is microalbuminuria, which is defined as albumin excretion rate (AER) of 30–300 mg/24 hour or albumin/creatinine ratio (ACR) of 2.5–25 mg/mmol.

Persistent microalbuminuria is shown to predict end-stage proteinuria and higher macrovascular complications. Routine screening is recommended from the age of 11 years in those with more than 2 years of diabetes duration. Angiotensin converting enzyme inhibitors (ACEI) are recommended for use in children and adolescents with hypertension. They reduce the rate of progression of microalbuminuria to macroalbuminuria. They can also prolong the time to end-stage renal disease. The role of ACEI in those with no hypertension is not clear as there is a risk of side effects of therapy.

Retinopathy

Retinopathy is the most common microvascular complication in type 1 diabetes in children. The incidence of background retinopathy increases to 50% at 10–15 years after diagnosis and up to 80% after 15 years diabetes duration. The changes can be attributed to chronic hyperglycemia, vascular damage and leakage, neovascularization, hemorrhage and ischemia. Increased vascular permeability causes edema and hard-exudates whereas arterial occlusion causes microaneurysms, soft exudates and hemorrhages. The growth of new blood vessels can cause vitreous hemorrhage and retinal detachment.

Retinopathy can be classified into (1) *background retinopathy* which involves microaneurysms with or without dot-blot hemorrhages and (2) *proliferative retinopathy* which involves growth of new vessels and fibrous tissue. Fluorescein angiography is used to assess the severity of retinopathy.

A baseline screening is recommended at the time of diagnosis. Regular annual evaluations are recommended from 10 years of age or 5 years after diagnosis of diabetes. Enalapril at a dose of 5–10 mg daily is known to slow the progression of retinopathy. In children with proliferative retinopathy, retinal photocoagulation is used to prevent neovascularization. In vitreous hemorrhage or detached retina, vitrectomy may need to be performed.

Neuropathy

Although symptomatic neuropathy is rarely seen in children with diabetes, subclinical neuropathy has been reported in as many as 50% of adolescents. Assessment of peripheral sensory function of the great toe should be done at each clinical visit. Diabetic neuropathy can be divided into: (1) peripheral neuropathy, which includes motor and sensory disturbances and (2) autonomic neuropathy, which results in gastrointestinal, cardiovascular, vasomotor instability and hypoglycemia unawareness.

1. *Peripheral neuropathy* Clinical symptoms of peripheral neuropathy include bilateral numbness and paresthesias, especially pain and burning in the lower extremities, which is much worse at night. Neurological examination of ankle reflexes, vibration and light touch sensation may show abnormal findings. Mononeuropathies in the form of carpal tunnel syndrome, palsy of the peroneal nerve, palsy of the third cranial nerve and proximal nerve conditions such as diabetic amyotrophy can be found in some cases.
2. *Autonomic neuropathy* Autonomic neuropathy can cause postural hypotension, vomiting, diarrhea, bladder paresis, impotence, sweating abnormalities and impaired light reflex. Abnormal heart rate responses and prolonged QT intervals have been associated with increased risk of sudden death.

Macrovascular Complications

Individuals with diabetes have 2–4 times higher risk of developing cardiovascular disease. Other factors such as smoking, hypertension, dyslipidemia, renal dysfunction and hyperglycemia increase the risk even further. Patients with vascular complications have high levels of endothelin-1 and apolipoprotein B. Presence of proteinuria is also a significant risk factor and treatment with ACE inhibitor is shown to result in risk reduction of myocardial infarction, cardiovascular deaths and stroke.

Hyperlipidemia

Children with low-density lipoprotein (LDL) cholesterol levels more than 160 mg/dL require pharmacologic intervention. Efforts to improve diet and exercise should always be initiated before starting medication. Statins are the first drug of choice and can be used in children above 10 years of age. Liver enzymes should be checked before starting treatment and lipid levels monitored frequently. Atorvastatin 10 mg/day is commonly used for high LDL cholesterol levels and fenofibrate at a dose 48 mg/day is used for increased triglyceride levels.

Hypertension

Hypertension is a significant risk factor for developing cardio-vascular morbidity. Hypertension in children is defined as average systolic or diastolic blood pressure consistently greater than 95th percentile for age, sex and height on three separate occasions. Hypertension requires treatment with ACE inhibitors such as enalapril at a dose of 5–10 mg daily and titrated until blood pressure is normalized. Salt restriction and 30–60 min of daily exercises is also advised.

MORE ON THIS TOPIC

Acerini C, Craig ME, de Beaufort C, et al. Introduction to ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes. 2014;15:1-3.

Donaghue KC, Chiarelli F, Trotta D, et al. Microvascular and macrovascular complications associated with diabetes in children and adolescents. Pediatric Diabetes. 2009:10:195-203.

Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child. 2004;89:188-203.

Kordonouri O, Maguire AM, Knip M, et al. Other complications and conditions associated with diabetes in children and adolescents; ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. Pediatric Diabetes. 2009:10:204-10.

Wolfsdorf MB, Glaser N, Sperling MA. Diabetic Ketoacidosis in infants, children and adolescents. Diabetes Care. 2006;29:1150-59.

IN A NUTSHELL

1. The important acute complications of diabetes mellitus in children include diabetic ketoacidosis and hypoglycemia.
2. Management of diabetic ketoacidosis includes avoidance of overzealous fluid and unnecessary alkali administration, to avoid the dreaded complications of cerebral and pulmonary edema. Attention to electrolyte balance, sensorium and the presence of infection are important.
3. Avoidance of severe hypoglycemia requires attention to patient education, particularly the nutritive values of foods and the effects of unplanned exercise.
4. Chronic complications can be classified as either microvascular (e.g., retinopathy, nephropathy, and neuropathy) or macrovascular (e.g., cardiovascular disease, cerebrovascular accidents, and peripheral vascular disease).
5. Screening for complications starts by about 2–5 years of duration of type 1 diabetes. Early intervention for hypertension, microalbuminuria, retinopathy and surveillance for foot care and neuropathy are helpful in delaying or minimizing progression.
6. The best option for chronic complications, however, is primary prevention by maintaining excellent blood glucose and blood pressure control and avoiding smoking and hyperlipidemia.

Chapter 44.25
Bone Mineral and Hormone Physiology
Philip G Murray, M Zulf Mughal

Physiological regulation of calcium levels is essential for the maintenance of health as abnormalities in calcium levels can lead to seizures and arrhythmia. In the longer term, intake and absorption of calcium and phosphate is required for the mineralization of the growth plate in osteoid (unmineralized bone matrix). Abnormalities in the pathways involved in calcium and phosphate regulation lead to a broad spectrum of clinical disorders, which are discussed in the next few chapters, but an understanding of the normal physiology is essential to clinical assessment of bone biochemistry.

CALCIUM

Serum concentrations of ionized calcium are closely regulated within a range of 1.1–1.3 mmol/L. In blood, calcium exists as an ionized fraction (~48%), protein bound fraction (~40%) and as calcium bound to other ions such as phosphate, lactate, citrate and bicarbonate (~12%). Measurement of total calcium rather than ionized calcium is common. Total calcium levels are significantly affected by the protein bound component, which is mainly bound to albumin. Thus, the total calcium concentration should be corrected for albumin concentration using the formula below, although modern analyzers provide corrected Ca values:

- Corrected Ca^{2+} mmol/L = Total Ca^{2+} mmol/L + (40 – albumin g/L × 0.02)

Where conventional rather than SI units are used then the formula required is:

- Corrected Ca^{2+} mg/dL = [0.8 × (4 – albumin g/dL)] + Total Serum Ca^{2+}

Over 99% of the body's calcium stores are held within the bone. Although calcium is essential for bone strength, the consequences from hypo/hyper-calcemia (e.g., arrhythmias, seizures, tetany) are sufficiently serious that the body acts to maintain serum calcium levels within the set range rather than to maintain skeletal mineralization. Maintenance of serum calcium concentrations requires adequate nutritional intake of calcium, vitamin D, parathyroid hormone secretion, and activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [achieved by CaSR signaling, parathyroid hormone (PTH) secretion and the 1 α hydroxylase enzyme]. Within the gastrointestinal tract calcium is transported from the gut lumen into serum via both paracellular and transcellular routes. Paracellular transport of calcium is mediated by claudin 16. For the transcellular route, active transport into the cell is achieved by transient receptor potential cation channel subfamily 5 members 5 and 6 (TRPV5 and TRPV6).

Parathyroid Glands

Parathyroid gland's size, number and location can be highly variable. Typically there are four parathyroid glands arranged as two sets of paired glands adjacent to the posterior thyroid. The superior glands are derived from the fourth branchial arch and the inferior glands from the third branchial arch. Ectopic parathyroid glands can be present in the thyroid gland, carotid sheath, within the mediastinum, along the thyrothymic ligament or within the thymus. Normal parathyroid glands are 5–10 mm in length and 2–4 mm in width weighing 20–40 mg. More than four parathyroid glands are present in ~13% of individuals. Genes known to be essential for normal parathyroid development include: *GCMB*, *SOX3*, *TBCE* and *GATA3*. Mutations in all these genes can lead to hypoparathyroidism.

Calcium Sensing Receptor

The calcium sensing receptor (CaSR) is a 1078 amino acid protein expressed in the chief cells of the parathyroid glands and in renal epithelial cells of the distal nephron. The CaSR exists as dimers with disulfide bonds linking the extracellular domains with each CaSR dimer containing multiple calcium binding sites within the extracellular domain. Binding of calcium triggers signal transduction via G proteins, which leads to a reduction in cAMP concentrations and activation of protein kinase A. The net result of CaSR signal transduction in the parathyroid is to increase the synthesis and secretion of PTH. Within the kidney CaSR activity acts to directly inhibit calcium reabsorption.

Magnesium binds to the CaSR in a fashion similar to calcium but is less potent at inducing activation of signal transduction. The adenylate cyclase activity of the G-protein associated with the CaSR is dependent upon intracellular magnesium concentrations and severe magnesium depletion can lead to impaired CaSR activity (and hence impaired PTH secretion).

Within the renal collecting ducts, the CaSR co-localizes with aquaporin 2, a channel responsible for water reabsorption under the control of ADH. Activation of CaSR leads to reduced Aquaporin 2 expression and hence, reduced ADH mediated water reabsorption. Hypercalcemia therefore leads to reduced water reabsorption and polyuria. This effect is intended to reduce urinary calcium concentration and protect from nephrolithiasis.

Parathyroid Hormone

Parathyroid hormone is an 84 amino acid peptide hormone secreted from the chief cells of the parathyroid gland in response to low extracellular calcium levels. It acts on the parathyroid hormone receptor, a G protein coupled receptor containing seven transmembrane domains in addition to intracellular and extracellular domains. Only the first 23 N-terminal amino acids of PTH are required to activate the PTHR. Signal transduction occurs via Gsα, cAMP and activation of protein kinase A. Parathormone keeps serum calcium within a narrow range by enhancing one hydroxylase enzyme activity (and thus 1,25 dihydroxyvitamin D mediated calcium absorption in the gut) and calcium reabsorption in the kidney, and causing resorption from the bone.

Vitamin D

Vitamin D is available in two distinct forms—ergocalciferol (vitamin D_2) which is present in some plants and fungi and cholecalciferol (vitamin D_3) which is produced in the skin and present in fish oils. The major source of vitamin D_3 is via the action of sunshine on skin. Ultraviolet (UV) light between 280–310 nm converts 7-dehydrocholesterol into vitamin D_3 (cholecalciferol). The 25-hydroxylase enzymes (5 distinct enzymes, the most important of which is CYP2R1) in the liver convert vitamin D_3 to 25-hydroxy vitamin D_3. Dietary intake of vitamin D_2 (ergocalciferol) generally contributes little to the body's stores of vitamin D unless significant amounts of fortified foods are consumed. Serum measurements of vitamin D sufficiency currently measure total 25-hydroxyvitamin D (D_2 or D_3). Vitamin D sufficiency is commonly defined as a serum 25-hydroxyvitamin D level > 50 nmol/L (25 ng/mL). 25-hydroxyvitamin D circulates in the serum bound to vitamin D binding protein.

Factors affecting serum levels of 25-hydroxyvitamin D levels mediate their effects via altering exposure to UV light in the spectrum and include: skin color (increased melanin leads to

reduced UV absorption), latitude (reduced sunlight exposure with increasing latitude), altitude, pollution, use of sunscreen, cultural influences on clothing reducing or increasing skin exposure to sunshine, and outdoor exposure to sunshine (glass blocks light in the UV spectrum essential to produce vitamin D_3).

Within the kidney, 25-hydroxyvitamin D can be converted either to 1,25-dihydroxyvitamin D or 24, 25-dihydroxyvitamin D. 1,25-dihydroxyvitamin D is produced by the action of 1-α hydroxylase and is the metabolically active vitamin D. The activity of 1-α hydroxylase is stimulated by PTH and low serum phosphate levels. Fibroblast growth factor 23 (FGF23), which is mainly derived from osteocytes down regulates the activity of 1-α hydroxylase. Serum 1,25-dihydroxyvitamin D concentrations inhibit the activity of 1-α hydroxylase in a negative feedback loop. In addition to its presence in the kidney 1-α hydroxylase is also present in bone, placenta, T-lymphocytes and macrophages as well as several cancers. The 1,25-dihydroxvitamin D produced in these tissues acts in an autocrine manner while that produced in the kidney acts in both an autocrine and paracrine manner.

In addition to the conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D it can also be converted by 24-hydroxylase (CYP24A1) to the inactive metabolite 24, 25-dihydroxyvitamin D. 24-hydroxylase is inhibited by PTH and stimulated by FGF23. **Figure 1** summarizes the generation and metabolism of vitamin D.

The effects of 1,25-dihydroxyvitamin D are mediated via the vitamin D receptor (VDR), a member of the nuclear hormone receptor superfamily encoded for by a gene located on chromosome 12q12. Binding of the VDR to 1,25-dihydroxyvitamin D leads to formation of heterodimers between the ligand bound VDR and one of the Retinoid X Receptors. These heterodimers translocate to the nucleus and bind to vitamin D response elements initiating transcription of a set of vitamin D dependent genes. Vitamin D signal transduction leads to:

1. Increased gastrointestinal absorption of calcium
2. Increased gastrointestinal absorption of phosphate
3. Increased renal absorption of calcium
4. Stimulates differentiation of osteoclasts
5. Suppresses PTH production.

Figure 2 summarizes the detection and response to hypocalcemia leading to increased 1,25-dihydroxyvitamin D.
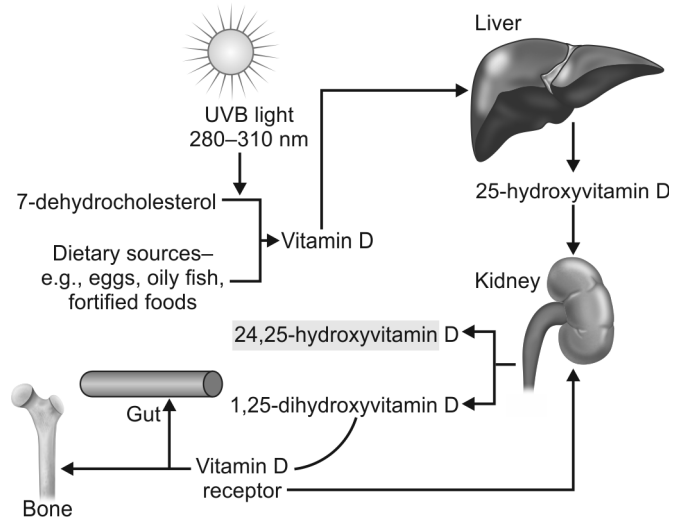
Figure 1 Metabolism of vitamin D. Vitamin D generated by the action of sunlight or consumed in the diet is hydroxylated in the liver to 25-hydroxyvitamin D. It is then converted in the kidney to active (1,25-dihydroxyvitamin D) or inactive (24,25-dihydroxyvitamin D) metabolites. The actions of 1,25-dihydroxyvitamin D in the gut, bone and kidney are mediated via the vitamin D receptor
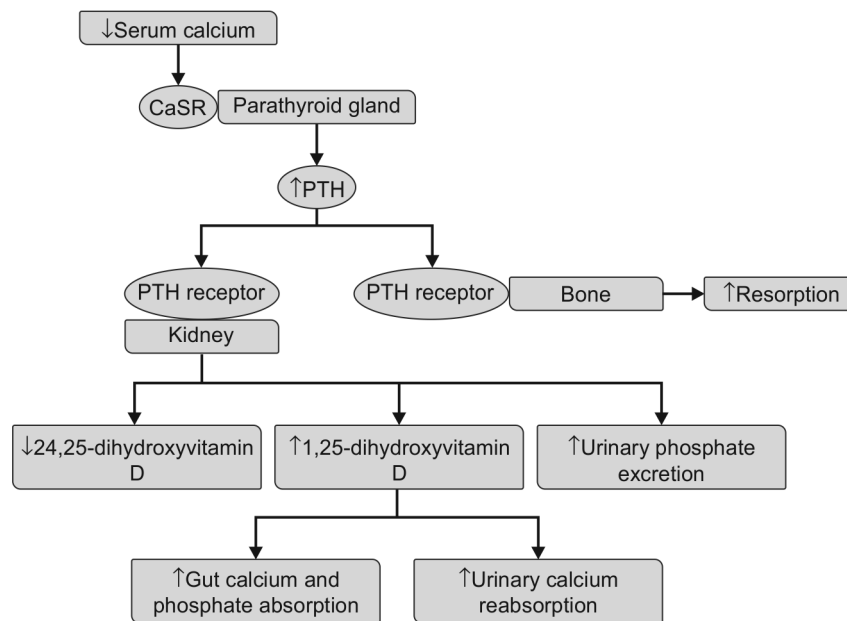
Figure 2 Physiological response to changes in serum calcium. A drop in serum calcium is detected by the calcium sensing receptor and leads to increased secretion of PTH. PTH acts on bone to increase resorption and release calcium. PTH also acts on the kidney to increase both urinary phosphate excretion and conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which acts to increase gut and urinary calcium reabsorption
Abbreviations: CaSR, calcium sensing receptor; PTH, parathyroid hormone.

PHOSPHATE

As with calcium, the majority of the body's phosphate is stored in bone. Intracellular phosphate is involved in many important signaling and metabolic pathways, while in plasma phosphate circulates as phospholipids and free inorganic phosphate.

The key regulatory molecule of extracellular phosphate concentrations is Fibroblast Growth Factor 23 (FGF23). FGF23 is produced in bone, mainly by osteocytes, however, the mechanisms through which the extracellular phosphate concentrations are sensed is currently unknown. The *FGF23* gene encodes a 251 aa protein including a 24 residue N-terminal signal peptide. After cleavage of the signal peptide, the mature FGF23 peptide can be cleaved at the RXXR site (amino acids 176–179) by the proprotein convertases (subtilin/furin) into two inactive components. Glycosylation by polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) prevents this degradation of FGF23 and allows it to act upon its receptor, which is present in the renal tubules.

The receptor for FGF23 is the fibroblast growth factor receptor 1 with the cofactor Klotho, both of which are required for the action of FGF23. Activation of this receptor leads to increased renal tubular phosphate excretion by increasing translocation of the NaPi-IIc sodium/phosphate transporter to the basolateral membrane of the renal epithelial cells. This leads to sodium reabsorption and phosphate excretion. This transporter is encoded by the *SLC34A3* gene. In addition, in increasing renal phosphate excretion FGF23 also increased degradation of 1,25-dihydroxyvitamin D.

In addition to serum phosphate concentrations FGF23 production is also controlled by the phosphate-regulating gene with homologies to endopeptidases on X-chromosome (*PHEX*) and dentin matrix protein 1. PHEX promotes cleavage of FGF23 while DMP1 inhibits FGF23 secretion. A summary of FGF23 activity and control is in **Flow chart 1**.

MAGNESIUM

Magnesium is required for secretion of PTH and deficiency can lead to a functional hypoparathyroidism. Absorption occurs in the small intestine is via the transient receptor potential cation family, subfamily M, members 6 and 7 (TRPM6 and TRPM7) as well as an Na^+/K^+ATPase. Within the kidney, passive reabsorption of magnesium occurs in the loop of Henle, via caudin 16.

MORE ON THIS TOPIC

Allgrove J. Physiology of calcium, phosphate and magnesium. In: Allgrove J, Shaw N. Calcium and Phosphate Disorders in Children and Adolescents. Basel: Karger; 2009. pp. 8-31.

Calcium Sensing Receptor database. From: http://www.casrdb.mcgill.ca. Accessed December 4, 2014.

Christov M, Juppner H. Insights from genetic disorders of phosphate homeostasis. Semin Nephrol. 2013;33:143-157.

Flow chart 1 Serum phosphate mechanisms influence FGF23 secretion via an unknown mechanism. FGF23 is degraded to inactive fragments by subtilin/furin, a process that is increased by PHEX. Glycosylation by GALNT3 prevents this degradation. FGF23 acts on a receptor containing FGF1R and co-factor Klotho, to increase urinary phosphate excretion via the sodium phosphate transporter NaPi-IIc. FGF23 also acts to increase degradation of 1,25-dihydroxyvitamin D
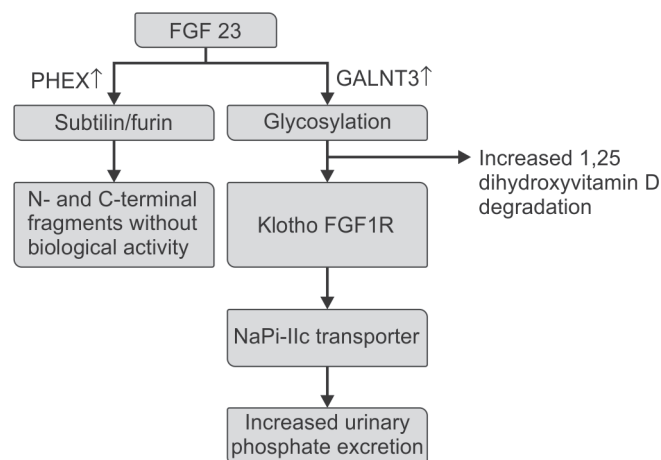
Abbreviations: FGF, fibroblast growth factor; PHEX, phosphate-regulating gene with homologies to endopeptidases on X-chromosome; GALNT3, polypeptide N-acetylgalactosaminyltransferase 3.

Gensure RC, Gardella TJ, Juppner H. Parathyroid hormone and parathyroid hormone-related peptide, and their receptors. Biochem Biophys Res Commun. 2005;328:666-78.

Kato S. The function of vitamin S receptor in vitamin D action. J Biochem. 2000;127:717-22.

IN A NUTSHELL

1. Serum calcium levels are sensed by the calcium sensing receptor on the chief cells of the parathyroid gland and control secretion of parathyroid hormone.
2. The major source of vitamin D is production in the skin induced by UV light exposure.
3. Parathyroid hormone acts to serum calcium levels by increasing the conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D.
4. 1,25-dihydroxyvitamin D acts via its receptor to increase gastrointestinal absorption of calcium and phosphate.
5. FGF23 acts to increase phosphate excretion in the kidney via a receptor composed of FGF1R and Klotho.
6. Magnesium is required for secretion of PTH and deficiency can lead to a functional hypoparathyroidism.

Chapter 44.26
Calcium Disorders
Shaila Sukthankar, Raja Padidela

Serum calcium is maintained within a narrow normal range, and the consequences of hypo- and hypercalcemia are serious. Hypocalcemia is a commonly encountered entity in the pediatric age group, particularly in neonates.

HYPOCALCEMIA

Hypocalcemia is defined as serum calcium (Ca) level below the lower limit of the normal range of 8.5–10.5 mg/dL (2.12–2.62 mmol/L). Hypocalcemia can occur at any age but is much more common in the neonatal period. The causes of hypocalcemia in children are listed in **Box 1**. *Hypomagnesemia* may lead to hypocalcemia due to impaired parathyroid hormone secretion and/or end organ resistance, and hence it is important to promptly recognize and treat it concomitantly.

Clinical Symptoms

Neonates Jitteriness, irritability, stridor, apnea, tetany, and generalized or focal convulsions.

Older child Mild hypocalcemia is associated with numbness and tingling sensation in the circumoral region, fingers and toes. Severe hypocalcemia can cause muscle cramps, tetanic carpopedal spasm, laryngospasm with stridor, and convulsions.

Cardiovascular manifestations include hypotension, heart failure and arrhythmias. An electrocardiogram will show prolonged Q-T interval.

BOX 1 Causes of hypocalcemia in childhood

- Increased skeletal need or inadequate supply of calcium
  – Early neonatal hypocalcemia
  – Malabsorption
  – Hungry bone syndrome, e.g., postparathyroidectomy, after rapid healing of severe vitamin D deficiency/dependency rickets
- Decrease in relative ionized calcium concentration
  – Chelation, e.g., blood transfusion
  – Respiratory or metabolic alkalosis
- Phosphate overload
  – Excessive phosphate intake (cow's milk in the neonate)
  – Acute or chronic renal failure
  – Crush injuries and rhabdomyolysis
- Hypoparathyroidism and parathyroid hormone (PTH) resistance
  – Transient (secondary to maternal hypercalcemia)
  – Familial hypocalcemic hypercalciuria (activating mutations of the calcium sensing receptor)
  – Congenital agenesis and hypoplasia of the parathyroid glands [DiGeorge syndrome, HDR (hypoparathyroidism, deafness and renal dysplasia) syndrome, Kearns–Sayre syndrome, Pearson syndrome, mutations of the *GCMB* gene]
  – Idiopathic hypoparathyroidism
  – Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)
  – Post-thyroidectomy or parathyroidectomy
  – Radiation to the neck
  – Iron deposition in parathyroid glands in thalassemia major
  – Pseudohypoparathyroidism (maternally inherited *GNAS1* mutations or imprinting defect).

Clinical Signs

Latent tetany can be elicited by the *Chvostek sign*—a twitching of the facial muscles in response to gentle tapping over the branches of the facial nerve anterior to the earlobe, but below the zygomatic arch. The *Trousseau sign*, elicited by inflating sphygmomanometer pressure to 10 mm Hg above systolic blood pressure and looking for carpal spasm over 3 minutes is more painful and should be avoided in children.

Neonatal Hypocalcemia

Early Neonatal Hypocalcemia

It typically occurs between 1 and 4 days of age in preterm infants, infants of diabetic mothers and asphyxiated infants. It can be due to abrupt postpartum termination of the maternal-to-fetal calcium supply; impaired secretion of parathormone (PTH) in response to hypocalcemia; or delay in establishing milk feeds in sick infants. Transfusion of large volumes of citrate containing donor blood can chelate calcium ions and lead to an acute decrease in ionized calcium. Over-correction of acidosis with bicarbonate therapy or through mechanical over-ventilation may also lead to a rapid fall in serum ionized calcium concentration. Infants born to diabetic mothers are prone to hypomagnesemia, which in turn can lead to hypocalcemia.

Late Neonatal Hypocalcemia

It occurs in apparently healthy full term infants between 5 and 10 days of age. Common causes include the following:

Transient hypoparathyroidism in infants born to mothers with unrecognized hypercalcemia during pregnancy—Increased materno-fetal calcium transport in utero (fetal hypercalcemia) is believed to suppress the fetal parathyroid glands, which are unable to maintain normal calcium concentration after birth.

Maternal severe vitamin D deficiency (especially if they are breastfed without concomitant vitamin D supplements)—Breastmilk is a poor source of vitamin D if the mother's vitamin D status is not optimal. These infants have low serum 25-hydroxyvitamin D and raised serum PTH. Disorders associated with vitamin D deficiency are discussed in the next chapter.

High phosphate load (cow's milk contains six times as much phosphorus as human milk)—This can overwhelm the capacity of the neonatal kidney to excrete phosphate, with subsequent hypocalcemia.

Childhood Hypocalcemia

Hypoparathyroidism

Hypoparathyroidism is characterized by hypocalcemia, hyper-phosphatemia and undetectable serum PTH in patients with normal renal function and absence of vitamin D deficiency. Causes are discussed further:

Congenital Agenesis or Hypoplasia of The Parathyroid Glands

DiGeorge syndrome (22q deletion syndrome) Hypoparathyroidism is associated with distinctive facial features, congenital heart disease, thymic aplasia with T-cell dysfunction, velopharyngeal dysfunction and developmental delay. Age of presentation can vary depending on severity of hypoparathyroidism. Some can manifest transient hypoparathyroidism during rapid phases of growth during infancy and puberty when calcium requirements are high.

Others Parathyroid gland development can be impaired in an autosomal dominant disorder of hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome caused by mutations in the *GATA3* gene. An autosomal recessive mutation of the *GCMB* transcription factor causes early neonatal hypoparathyroidism.

Autoimmune Destruction of the Parathyroid Glands
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) An autosomal recessive disorder caused by lack of a functional product of the autoimmune regulator (*AIRE*) gene located on chromosome 21q22.3. It is characterized by autoimmune-mediated failure of multiple endocrine glands (parathyroid glands, adrenals, gonads, pancreatic islet cells, gastric parietal cells and thyroid). Age of onset varies but typically chronic mucocutaneous candidiasis presents at around 5 years of age, followed by hypoparathyroidism at around 8 years of age and adrenal failure at around 12 years of age.

Parathyroid Hormone Resistance (Pseudohypoparathyroidism)
This is characterized by hypocalcemia, hyperphosphatemia and markedly elevated serum PTH concentration due to an end organ resistance to PTH. Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders associated with PTH resistance. Children with PHP are further classified according to the presence (PHP-1a) or absence (PHP-1b) of clinical features of Albright hereditary osteodystrophy (AHO) round face, obesity, short stature, brachydactyly, ectopic ossification and developmental delay.

Pseudohypoparathyroidism-1a (PHP-1a) is caused by heterozygous inactivating mutations in the gene encoding for the G protein α-subunit (*GNAS1*). It also results in resistance to thyroid stimulating hormone and gonadotropins. The mutation may be present in family members of patients with PHP-1a. When there are physical stigmata of AHO but biochemistry is normal, the condition is referred to as pseudopseudohypoparathyroidism (PPHP). PHP-1a occurs when the *GNAS1* mutations are inherited maternally, whereas paternally inherited mutations lead to PPHP. Patients with PHP-1b have the symptoms, signs and biochemical features of PTH-resistance but lack the phenotypic features of AHO.

Familial Hypercalciuric Hypocalcemia
This is an autosomal dominantly inherited condition caused by activating mutations in the calcium sensing receptor (CaSR) gene. Such mutations result in an altered calcium sensing *set point* in the parathyroid glands, so that PTH secretion is blocked by lower than *normal* serum calcium concentration. These patients have mild to moderate hypocalcemia, moderately elevated serum phosphorous concentration with relative hypercalciuria. Serum PTH concentration is inappropriately low for the serum calcium concentration.

Severe Vitamin D Deficiency
Disorders associated with vitamin D deficiency are discussed in detail in the next chapter.

Treatment
Intravenous 10% calcium gluconate solution (0.2 mL/kg) should be administered to infants with acute symptomatic hypocalcemia (e.g., seizures). This is infused over 10 minutes as rapid injection can cause cardiac arrhythmias. Placement of the intravenous catheter in a large vein avoids extravasation into the subcutaneous tissues with resulting tissue necrosis and permanent scarring.

Once the patient is asymptomatic, a maintenance infusion of 10% calcium gluconate (8–40 mg calcium/kg/day or 1–5 mL/kg/day); or oral calcium supplements (50–75 mg/kg/day of elemental calcium in four divided doses) can be prescribed. For older children and adolescents, the maximum dose of oral calcium supplements is 2 g/day.

In infants with hypocalcemia secondary to magnesium deficiency, IM 50% magnesium sulfate solution (100 mg/kg or 0.2 mL/kg/dose) is used. Two injections, 12 hours apart, are sufficient for most cases of neonatal hypocalcemia. Patients with primary defects of magnesium metabolism require long-term treatment with oral magnesium supplements.

For treatment of chronic hypocalcemia associated with parathyroid deficiency/resistance, calcitriol (1,25-dihydroxyvitamin D) and alfacalcidol (1-α-hydroxyvitamin D) are used. Calcitriol is started at the initial oral dose of 15 ng/kg/day (maximum 1.5 µg). It has shorter half-life and hence needs to be given twice daily. Alfacalcidiol can be started at 25 ng/kg (maximum 2.0 µg) and can be administered as a single dose.

The aims of treatment of chronic hypocalcemia are to maintain serum calcium concentration in the low normal (rather than normal or high normal level) range to avoid potential hypercalciuria or nephrocalcinosis (associated with reduced renal tubular reabsorption in the absence of PTH action), while also avoiding hypercalcemia or nephrolithiasis. It is recommended that serum calcium and spot urine calcium to creatinine ratio are measured every 4–6 months. Oral calcium supplements may be necessary if the child's diet is deficient in calcium-rich dairy products. Net absorption of calcium salts plateaus off above a single dose of 500 mg. Therefore, multiple divided doses of calcium supplements are preferable.

HYPERCALCEMIA

Hypercalcemia develops when the rate of calcium entry into the extracellular fluid exceeds the kidneys' capacity for its excretion. Mechanisms include increased absorption of calcium from the gastrointestinal tract, increased release of calcium from the skeleton or decreased excretion of calcium from the kidneys **(Box 2)**.

BOX 2 Causes of hypercalcemia in childhood

- Increased intestinal calcium absorption
  - William syndrome (microdeletion of chromosome 7q11.23)
  - Idiopathic infantile hypercalcemia (inactivating mutation of CYP24A1)
  - Vitamin D intoxication
  - Vitamin A intoxication
  - Granulomatous disorders, e.g., sarcoidosis, tuberculosis
  - Subcutaneous fat necrosis
- Decreased renal calcium excretion
  - Thiazide diuretics
  - Primary hyperparathyroidism
- Increased bone resorption
  - Immobilization
  - Primary and tertiary hyperparathyroidism
  - Malignancy
- Familial hypercalcemic hypocalciuria
  - Autosomal dominant, caused by inactivating mutations of the calcium sensing receptor
- Others
  - Jansen metaphyseal chondrodysplasia
  - Dietary phosphate deficiency (breastfed infants).

Etiopathogenesis

Increased Intestinal Calcium Absorption

William syndrome Many infants develop symptomatic hypercalcemia during the first year of life, the precise cause is not known. PTH concentration is suppressed.

Idiopathic infantile hypercalcemia (IIH) This rare condition becomes apparent during the first year of life. Recently, homozygous or compound heterozygous loss-of-function mutation in the *CYP24A1* gene (it breaks down 1,25-dihydroxyvitamin D_3 into an inactive metabolite) has been found in IIH.

Subcutaneous fat necrosis It is thought that the ectopic 1,25-dihydroxyvitamin D produced by inflammatory, mononuclear cell infiltrates in these lesions increases gastrointestinal calcium absorption. Hypercalcemia tends to be self-limiting but needs treatment as described below:

Vitamin D intoxication This can arise from inadvertent chronic overdose of the vitamin given for therapeutic purposes or as a result of ill-informed self- (or parent) administration of multivitamin preparations. Serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D are elevated and PTH is suppressed. Hypercalcemia and hypercalciuria can last for several weeks after stopping the supplements, because of deposition of ingested vitamin D in fat and muscle tissues.

Hyperparathyroidism (HPT)

Transient neonatal hyperparathyroidism Transient neonatal HPT occurs in infants born to mothers with untreated or inadequately treated hypoparathyroidism or pseudohypoparathyroidism. The decreased materno-fetal calcium transport in utero leads to fetal hypocalcemia, which in turn stimulates the fetal parathyroid glands and the high serum PTH with hypercalcemia persists for several weeks.

Primary hyperparathyroidism It is an exceedingly rare condition during childhood and usually manifests as part of multiple endocrine neoplasia (MEN 1). There is often a delay of months to years before the diagnosis is made and, therefore, patients often have nephrocalcinosis, nephrolithiasis, *brown tumors* and pathological fractures. Hypercalcemia occurs because of increased bone resorption and increased calcium absorption.

Tertiary HPT may occur due to autonomous hypersecretion of PTH in children with untreated secondary hyperparathyroidism (e.g., renal osteodystrophy). Treatment involves total parathyroidectomy.

Miscellaneous

Jansen metaphyseal chondrodysplasia This rare dominantly inherited disorder is caused by activating mutations of the PTH/PTHrP receptor and is characterized by short-limbed dwarfism, bowing of long bones, dysplastic growth plates and mild hypercalcemia. The picture resembles mild hyperparathyroidism but with low serum concentrations of PTH and PTH-related peptide (PTHrP).

Immobilization with skeletal demineralization Prolonged immobilization, for example, following burns, spinal cord injury, Guillain-Barré syndrome, can result in hypercalcemia through skeletal demineralization. Adolescents are particularly susceptible.

Familial hypocalciuric hypercalcemia (FHH) It is inherited in an autosomal dominant fashion. It is characterized by generally asymptomatic lifelong mild hypercalcemia and hypocalciuria. FHH is caused by heterozygous inactivating mutations in the calcium sensing receptor *(CaR)* gene, which result in altered calcium-sensing by the parathyroid glands, so that higher serum calcium concentrations are required to block PTH secretion. Urine calcium excretion is low despite increased serum calcium concentration, due to CaSR-mediated inhibition of calcium reabsorption in the kidney. Usually, no treatment is necessary. Homozygous inheritance of the mutation produces neonatal severe hyperparathyroidism.

Clinical Features

Symptoms of hypercalcemia in infants are often nonspecific and include feeding difficulties, vomiting, constipation, failure to thrive, irritability and hypotonia. Older children may present with anorexia, nonspecific abdominal pain, muscle weakness and neuropsychiatric symptoms. Polydipsia and polyuria may lead to dehydration and fever. Chronic hypercalcemia and accompanying hypercalciuria may predispose to nephrocalcinosis, nephrolithiasis and, if left untreated, to renal impairment.

Treatment

Treatment of symptomatic hypercalcemia includes general supportive measures to normalize serum calcium concentration and specific treatment of the underlying cause. Patients should avoid immobilization, which increases bone resorption and aggravates hypercalcemia. This is particularly important in adolescents.

Hydration and Sodium Diuresis

Intravenous isotonic saline (1–1.5 times the daily fluid allowance) helps to rehydrate the patient. An increase in urinary sodium also helps coupled urinary calcium excretion. Sodium diuresis can be enhanced with a loop diuretic (furosemide 1 mg/kg 12 hourly). Thiazide diuretics must be avoided as they impair urinary calcium excretion.

Reduction of Gastrointestinal Calcium Absorption

Reduction of dietary calcium (to approximately one-fourth to one-third of the recommended intake for age) and vitamin D intake (all preparations containing vitamin D must be discontinued and a sunblock cream be used to limit cutaneous vitamin D synthesis) is effective in reducing intestinal calcium absorption. Oral prednisolone (2 mg/kg/day, maximum dose, 60 mg/day) can also reduce absorption in vitamin D toxicity and cases with ectopic synthesis of 1,25-dihydroxyvitamin D (e.g., in sarcoidosis). Once hypercalcemia resolves, it is important to normalize the diet with respect to calcium and vitamin D.

Inhibition of Bone Resorption

The bisphosphonates inhibit osteoclastic bone resorption and are effective in the treatment of resorptive hypercalcemia. Intravenous pamidronate disodium (1 mg/kg/day, maximum 60 mg) can be infused over 4 hours and is usually administered every 2–3 days until serum calcium concentration normalizes.

Dialysis

Peritoneal or hemodialysis against low calcium dialysis solution is highly effective in lowering plasma calcium concentration. This is reserved for life-threatening hypercalcemia.

IN A NUTSHELL

1. Hypocalcemia is defined as serum calcium (Ca) level below the lower limit of the normal range of 8.5–10.5 mg/dL (2.12–2.62 mmol/L).
2. Serious manifestations include prolonged Q-T interval, hypotension, heart failure and arrhythmias, tetanic carpopedal spasm, laryngospasm with stridor, and convulsions.
3. Slow intravenous 10% calcium gluconate solution (0.2 mL/kg) through a large vein, should be administered to infants with acute symptomatic hypocalcemia. Maintenance infusion is with 10% calcium gluconate (8–40 mg calcium/kg/day or 1–5 mL/kg/day).
4. Hypomagnesemia may lead to hypocalcemia due to impaired parathyroid hormone secretion and/or end organ resistance.
5. Symptoms of hypercalcemia in infants are often nonspecific and if left untreated for a long time nephrocalcinosis, nephrolithiasis and renal impairment may supervene.
6. The principles of management of hypercalcemia include hydration and sodium diuresis, reduction of gastrointestinal calcium absorption, inhibition of bone resorption and dialysis.

MORE ON THIS TOPIC

Balasubramanian S, Shivbalan S, Kumar PS. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. Indian Pediatr. 2006;43: 247-51.

Davies JH, Shaw NJ. Investigation and management of hypercalcaemia in children. Arch Dis Child. 2012;97:533-8.

Ding D, Buckingham B, Levine M. Familial isolated hypoparathyroidism caused by a mutation in the gene for the transcription factor GCMB. J Clin Invest. 2001;108:1215-20.

Dudink J, Walther FJ, Beekman RP. Subcutaneous fat necrosis of the newborn: Hypercalcemia with hepatic and atrial myocardial calcification. Arch Dis Child Fetal Neonatal Ed. 2003;88:F343-9.

George J, Acharya SV, Bandgar TR, et al. Primary hyperparathyroidism in children and adolescents. Indian J Pediatr. 2010;77:175-8.

Mantovani G. Clinical review. Pseudohypoparathyroidism: diagnosis and treatment. J Clin Endocrinol Metab. 2011;96:3020-30.

Pollak MR, Brown EM, Estep HL, et al. Autosomal dominant hypocalcemia caused by a Ca^{2+}-sensing receptor gene mutation. Nat Genet.1994;8:303-7.

Schlingmann KP, Kauffman M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 2011;365:410-21.

Van Esch H, Groenen P, Nesbit M, et al. GATA3 haplo-insuffiency causes human HDR syndrome. Nature. 2000;406:419-22.

Zhou P, Markowitz M. Hypocalcemia in infants and children. Pediat Rev. 2009;30:190-2.

Chapter 44.27
Metabolic Rickets

Shaila Sukthankar, Raja Padidela

Rickets is a condition that typically occurs in growing children, due to lack of mineralization of osteoid matrix and the growth plate. Chronic hypophosphatemia is the final biochemical step in the evolution of all forms of rickets. It impairs apoptosis of the chondrocytes, which results in clinical and radiological features of rickets. This pathophysiological pathway is highlighted in **Flow chart 1**.

CALCIPENIC RICKETS

Nutritional Rickets

This results from inadequate synthesis of $1,25(OH)_2D$, often due to a lack of its precursor, $25(OH)D$, in diet or via dermal synthesis, and can be successfully treated with oral or parenteral vitamin D supplementation (see Section 22, Chapter 12 for a detailed discussion on nutritional rickets). In parts of the Indian subcontinent and Africa, rickets in children may also occur due to very low dietary calcium content leading to raised parathyroid hormone (PTH), despite only slightly reduced or normal concentrations of $25(OH)D$. Calcium supplements alone can completely heal the rickets, though additional vitamin D supplementation results in quicker healing.

Rickets of Non-nutritional Origin

Metabolic causes of rickets should be suspected when there is inadequate response to nutritional replacement of 2–3 months duration. They may also be suspected earlier in the presence of clues such as alopecia [*Vitamin D-dependent rickets* (VDDR type II)] and hypokalemia with nephrocalcinosis (renal tubular acidosis), among others **(Fig. 1)**.

1. *Vitamin D-dependent rickets type I (VDDR type I)* This autosomal recessive condition with the inactivating homozygous mutations of *CYP27B1* gene, leads to an impaired renal $1,\alpha$-hydroxylase enzyme activity and resultant low or undetectable $1,25(OH)_2D$ levels. Affected patients present
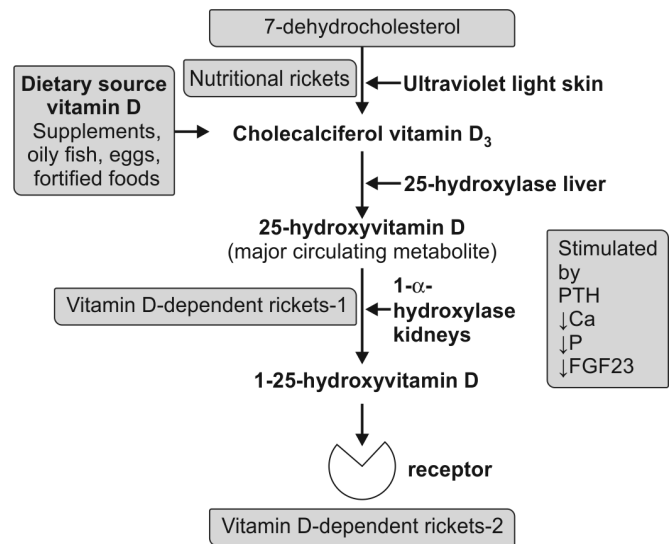
Figure 1 Vitamin D metabolism and rickets

with hypocalcemia and severe clinical features of infantile rickets. Treatment with 1α-hydroxyvitamin D (alfacalcidol) or calcitriol usually cures rickets but is needed lifelong.

2. *Vitamin D–dependent rickets type II (VDDR type II)* In this condition with homozygous mutations of vitamin D receptor gene, resistance to the biological actions of the active form of $1,25(OH)_2D$ leads to a clinical presentation very similar to VDDR type I. However, $1,25(OH)_2D$ levels are markedly elevated in these patients. Several mutations of the ligand binding domain (LBD) or the DNA-binding domain (DBD) have been reported to date, and are associated with partial/complete resistance to active vitamin D. Children with DBD mutations classically have total alopecia. Some may respond to large doses of calcitriol or 1α-hydroxyvitamin D (alfacalcidol); however, children with mutations causing severe resistance (e.g., DBD mutations) will usually heal only with high doses of oral and/or intravenous calcium.

3. *Other causes* of non-nutritional calcipenic rickets include malabsorption (both of calcium and vitamin D) secondary to liver and gastrointestinal disorders, distal renal tubular

Flow chart 1 Pathophysiology of rickets
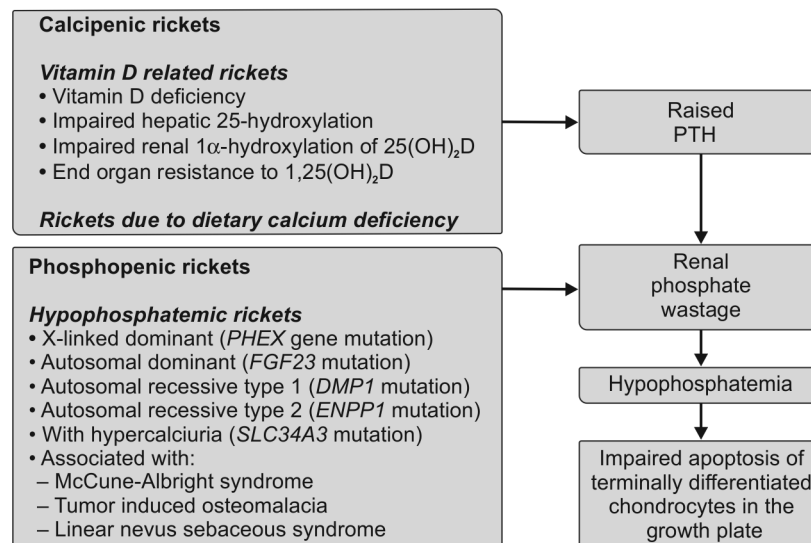
acidosis, and anticonvulsant-induced rickets (vitamin D supplements should be considered during phenytoin, carbamazepine and phenobarbitone therapy).

Clinical Features

Clinical features largely relate to the age at onset and the severity of rickets. Skeletal deformations are more likely to occur in infancy.

- Infants usually develop deformities in their weight-bearing limbs. For example, crawling babies have forearm deformities, whereas bowed legs (genu varum) or knock-knees (genu valgum) are more likely to develop in toddlers. Rickets may also be associated with faltering growth, frontal skull bossing, double malleoli and widened wrists.
- Rachitic rosary develops due to expansion of the costochondral junctions, and Harrison sulcus may be due to an inward pull of the diaphragm on softened rib cage. Pigeon chest appearance is due to forward projection of the sternum.
- Delayed tooth eruption and impaired tooth enamel can cause abnormal dentition. Bone pain may cause irritability in infants.
- Hypotonia and muscle weakness associated with vitamin D deficiency can delay early motor development. Severe vitamin D deficiency has been described to cause dilated cardiomyopathy which may be life-threatening.
- Vague symptoms of aches and pains in the lower limbs (after walking or playing games) and proximal muscle weakness (which may make climbing stairs a difficult task) are more common in adolescents. Tetany and muscular cramps are also more likely in this age than in infancy. Florid signs of rickets are rare. Bowlegs and knock-knees may rarely develop with very long-standing deficiency. Pelvic deformities occurring in adolescence may lead to difficult labor in future years.

Investigations

Radiological Features

These are evident most common at the rapidly growing ends of long bones and may include: (a) Loss of the crisp line at the ends of long bone (zone of provisional calcification)—it appears frayed or *brush-like*; can appear concave or *cup-shaped* in advanced stages; (b) Metaphyseal widening; and (c) Generalized osteopenia, subperiosteal bone resorption and, in severe cases, the so-called *brown tumors*—all suggestive of secondary hyperparathyroidism.

Biochemical Findings

Details of biochemical changes in rickets are presented in **Table 1**.

Treatment

It includes calcium and vitamin D supplements (see chapter on nutritional rickets), specific treatment of non-nutritional causes is described in relevant sections. Clinical symptoms, such as aches and pains, start to improve within 2 weeks, while in toddlers, the bone deformities resolve usually by 6 months. Full correction of bowed legs or knock-knees in the group with nutritional deficiency may take 1–2 years. Deformities of bones in adolescents do not heal completely and may require surgical correction of residual skeletal deformities. X-ray of the knees 6 months after starting treatment helps to monitor healing and progress.

PHOSPHOPENIC RICKETS

Normal levels of serum phosphate are required for various vital cellular functions as well as bone mineralization. Complex interactions between the gut, bones and the renal tubules maintain phosphate homeostasis. The gut absorption of dietary phosphate is enhanced by $1,25(OH)_2D$. PTH induces renal phosphate excretion. Over 85% of glomerular filtered phosphate is reabsorbed by the sodium dependent phosphate transporters in the proximal renal tubules.

Osteocytes produce FGF23 in response to high phosphate levels (and also raised $1,25(OH)_2D$), which then acts on the renal tubules by binding to the FGF receptor family (predominantly FGFR1c, with α-Klotho as coreceptor), to prevent phosphate reabsorption. FGF23 also inhibits renal 1α-hydroxylase suppressing the renal production of $1,25(OH)_2D$, thus reducing intestinal phosphate absorption **(Flow charts 2 and 3)**.

Flow chart 2 Regulation of serum phosphate

Table 1 Biochemical findings in rickets

	Ca	P	25-OHD	1,25(OH)₂	ALK	PTH	U-P	U-Ca
Vitamin D deficiency	N,↓	↓	↓	↓, N, ↑	↑	↑	↑	↓
Dietary caclium deficiency	N, ↓	↓	N	↑	↑	↑	↑	↓
VDDR, type1	N, ↓	↓	N	↓	↑	↑	↑	↓
VDDR, type 2	N,↓	↓	N	↑	↑	↑	↑	↓
XLH	N	↓	N	N*	↑	N	↑	↓
ADHR, ARHR1, ARHR2	N	↓	N	N*	↑	N	↑	↓
HHRH	N	↓	N	↑	↑	N, ↓	↑	↑
Tumor-induced osteomalacia	N	↓	N	N*	↑	N	↑	↓

Note that serum phosphate is reduced in all these forms of rickets
Abbreviations: VDDR, vitamin D-dependent rickets; XLH, X-linked hypophosphatemic rickets; ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; HHRH, hypophosphatemic rickets with hypercalciuria; Ca, serum calcium; P, serum phosphorus; 25-OHD, 25-hydroxyvitamin D; 1,25(OH)₂, 1,25, dihydroxyvitamin D; ALK, alkaline phosphatase; PTH, parathyroid hormone; U-P, urinary phosphate; UCa, urinary calcium; N, normal, ↑, increased; ↓, decreased; N*, within normal range but inappropriately low for the prevailing low levels of serum phosphate as high circulating levels of FGF23 down regulates 1-alphahydroxylase enzyme

Flow chart 3 Conditions associated with hypophosphatemia
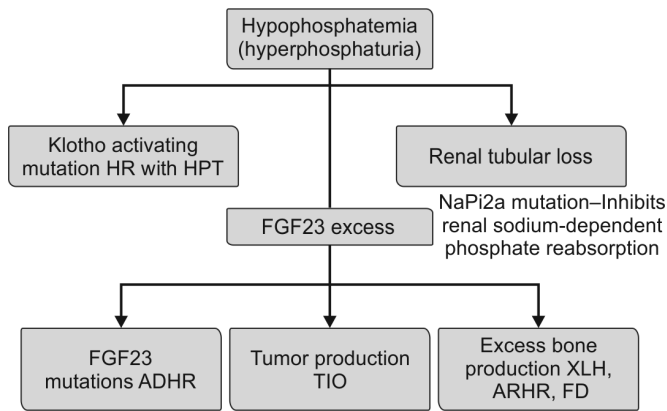
Abbreviations: FGF23, fibroblast growth factor-23; TIO, tumor induced osteomalacia; XLH, X-linked hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; FD, fibrous dysplasia; HR with HPT, hypophosphatemic rickets with hyperparathyroidism; HHRH, hypophosphatemic rickets with hypercalciuria.

Hereditary Hypophosphatemic Rickets Associated with Raised Serum FGF23 Concentration

X-linked Hypophosphatemic Rickets (XLH)

This is the most common inherited form of hypophosphatemic rickets (incidence 1:20,000), due to inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) on the Xp22.1 position on the short arm of the X chromosome. It leads to increased FGF23 concentration in circulation. Patients develop genu varum after a year of age. They may develop waddling gait secondary to coxa vara and/or an *in-toeing gait* due to medial tibial torsion. If untreated, children develop short stature with disproportionate shortening of the lower limbs. *Unlike in vitamin D deficiency rickets, hypotonia, myopathy and tetany are absent in this condition.* Spontaneous dental abscesses are known to occur even without dental caries. Skull shape distortion occurs due to premature cranial suture fusion, and may occasionally lead to raised intracranial pressure. Enthesopathy or heterotopic calcification of the tendons, ligaments and joint capsules occurs in older children.

The *clinical manifestations* of *X-linked hypophosphatemic rickets (*XLH) can vary, even with the same *PHEX* gene mutation in several family members. Radiological features include thick cortices and coarse trabeculae, and are worse in the lower limb bones. The metaphyseal cupping, widening and fraying, etc., is usually less marked than in calcipenic rickets.

Main *biochemical changes* in XLH include: Raised serum FGF23 concentrations; low serum phosphate concentration for age; increased renal phosphate excretion; normal serum 25(OH)D levels; inappropriately normal or low concentration of $1,25(OH)_2D$, despite low Pi levels (see above); normal serum calcium; no evidence of hypercalciuria or secondary hyperparathyroidism in untreated patients; and increased age-adjusted serum alkaline phosphatase activity.

Treatment

1. Oral phosphate supplementation—administered as neutral phosphate tablets in four to six divided doses. Joulie's solution can be given to infants and toddlers. Initiation of phosphate therapy invariable leads to abdominal pain and diarrhea. Initiating therapy at a smaller dose and gradually increasing it improves tolerance to side effects.

2. Administration of $1,25(OH)_2D$ (calcitriol) or $1\alpha\text{-}(OH)D$ (alfacalcidol)—increases intestinal phosphate and calcium absorption. It also helps prevent secondary hyperparathyroidism, which occurs if phosphate therapy is used alone. Alfacalcidol is administered once a day (25 ng/kg/day, increased slowly to 50 ng/kg/day, up to maximum 2 μg/day) until there is biochemical and radiological evidence of healing. Careful monitoring is necessary, to avoid secondary hyperparathyroidism, hypercalcemia, hypercalciuria and nephrocalcinosis. Raised plasma PTH level suggests either overtreatment with phosphate or undertreatment with alfacalcidol. If hypercalciuria or hypercalcemia is present, alfacalcidol (or calcitriol) should be temporarily stopped until urine calcium excretion and serum calcium concentration are back to normal. The treatment should then be restarted at 75%of the previous dose.

Preventative dental care, use of fissure sealants and topical fluoride applications can reduce the incidence of dental abscess formation.

The current form of therapy is far from ideal; complete healing of rickets rarely occurs because long-term compliance is often difficult. In patients who are particularly prone to developing hyperparathyroidism due to phosphate therapy, treatment with Cinacalcet, the calcimimetic agent, may help suppress PTH secretion. Despite medical treatment, some patients have residual skeletal deformities (e.g., severe genu varum) and may require surgical correction using epiphysiodesis or femoral/tibial osteotomies.

Preclinical studies in juvenile Hyp mice and in adults have shown that injection of a neutralizing FGF23 IgG1 antibody provides a more rational therapy for XLH patients. Current data demonstrates dose-dependent normalization of serum phosphate and $1,25(OH)_2D$ concentrations, improvement of longitudinal growth of the long bones, and healing of rachitic changes.

Autosomal Dominant Hypophosphatemic Rickets (ADHR; FGF23 Gene Mutations)

In this rare disorder, patients have mutations in the cleavage domain of *FGF23* that leads to impaired proteolytic inactivation of *FGF23*. This condition is often milder and may demonstrate remission of hypophosphatemia corresponding with decrease in previously raised FGF23 concentrations. The management is identical to that for XLH.

Autosomal Recessive Hypophosphatemic Rickets Type 1 (ARHR1; DMP1 Gene Mutations)

In this condition, inactivating mutations in the genes encoding for dentin matrix protein1 *(DMP1)* in osteocytes results in raised *FGF-23* concentrations. *DMP1* is involved in regulating mineralization and is also involved in transcription of FGF23 by osteocytes, though mechanisms remain unclear.

Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2; ENPP1 Gene Mutations)

Generalized arterial calcification of infancy (GACI) includes calcification of large and medium-sized arteries, myocardial infarction and often death in early childhood) is associated with homozygous inactivating mutations of the gene encoding for *ENPP1* (ecto-nucleotide pyrophosphatase/phosphodiesterase). Some survivors of GACI may have hypophosphatemic rickets associated with high plasma FGF23 concentrations. Further, understanding of these mechanisms is still required, and may shed light on the vascular calcification that occurs in other disorders with high FGF23 levels, such as chronic renal failure.

Hypophosphatemic Rickets Associated With McCune-Albright Syndrome/Fibrous Dysplasia (MAS/FD)

Almost half of MAS/FD patients develop hypophosphatemic rickets secondary to excess production of FGF23 in the dysplastic osteogenic cells of the fibrous lesions. Management is similar to that of XLH.

Tumor-induced Osteomalacia

This is associated with mesenchymal tumors which secrete FGF23, leading to increased renal phosphate loss, hypophosphatemia, and low serum $1,25(OH)_2D$ concentrations. Along with clinical signs of rickets, these patients develop bone pains, muscle weakness and pathological fractures. Identification of the offending tumors, often tiny, is often difficult. Anatomical as well as functional imaging, e.g., octreotide scintigraphy and selective venous sampling with measurement of FGF23, may help in locating the tumor site. Excision of these tumors leads to complete cure of the bone disease.

Linear Nevus Sebaceous Syndrome

Also called epidermal nevus syndrome, this rare and sporadic neurocutaneous syndrome can cause hypophosphatemic rickets due to raised serum FGF23 concentrations. Excision of the nevus results in decrease in serum FGF23 levels leading to clinical improvement.

Hypophosphatemic Rickets with Hypercalciuria (HHRH; *SLC34A3* Gene Mutations)

This rare autosomal recessive condition is caused by inactivating mutations in the gene that encodes for the renal sodium-phosphate cotransporter NaPi-IIc *(SLC34A3)*. It was first described in Bedouin families with consanguinity. HHRH is characterized by low serum phosphate with appropriately increased serum $1,25(OH)_2D$, and hypercalciuria due to increased absorption of calcium from the gut. Treatment with oral phosphate supplements alone results in

healing of rickets and improvement of hypercalciuria. Treatment with vitamin D analogs is not required, and is often harmful indeed, as it may cause nephrocalcinosis/recurrent nephrolithiasis.

IN A NUTSHELL

1. Chronic hypophosphatemia is the final biochemical step in the evolution of all forms of rickets.
2. Nutritional rickets occurs commonly due to either vitamin D deficiency (poor sun exposure and dietary inadequacy of the vitamin) or dietary calcium deficiency.
3. Metabolic causes of rickets should be suspected when there is inadequate response to nutritional replacement of 2–3 months' duration.
4. Calcium deficiency rickets includes nutritional, malabsorption, vitamin D dependent and renal rickets. Hypotonia, muscle weakness and tetany characterize these forms.
5. Phosphate deficiency rickets is caused by disorders which are accompanied by phosphorus leak at the kidneys, due to excess of circulating phosphaturic hormone FGF23. These forms are characterized biochemically by normal or only minimally elevated parathormone.
6. Complete bone healing during treatment of rickets takes 6–24 months.

MORE ON THIS TOPIC

Aggarwal V, Seth A, Aneja S, et al. Role of calcium deficiency in development of nutritional rickets in Indian children: a case control study. J Clin Endocrinol Metab. 2012;97(10):3461-6.

Bergwitz C, Juppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010;61:91-104.

Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011;26(7):1381-8.

Malloy PJ, Feldman D. Genetic disorders and defects in vitamin D action. Endocrinol Metab Clin North Am. 2010;39(2):333-46.

Tiosano D, Hochberg Z. Hypophosphatemia: The common denominator of all rickets. J Bone Miner Metab. 2009;27(4):392-401.

Chapter 44.28
Disorders with Bone Fragility
M Zulf Mughal

In this chapter, development of bone relevant to understanding of fractures in children is briefly reviewed. Besides fractures in otherwise healthy children, important primary and secondary causes of skeletal fragility in childhood are discussed. An introduction to assessment of bone health by dual-energy X-ray absorptiometry, and management of primary and secondary osteoporosis are briefly covered. Treatment of complex childhood bone disorders is outside the scope of this chapter.

BONE DEVELOPMENT

Bone is a highly specialized rigid tissue that must withstand the load-bearing requirements of the skeleton without fracturing. It consists of crystals of hydroxyapatite embedded within organic matrix, consisting largely of triple helical fibers of type 1 collagen. Skeletal development begins in utero and is dependent on an inherited genetic 'template' that is modified by mechanical loading, nutritional and endocrine environments. Linear growth is accompanied by increases in size (length and diameter), the amount of bone mass [bone mineral content (BMC)] contained within the periosteal envelope and strength of bones. During the adolescent growth spurt, the rapid increase in linear growth precedes the accrual of bone mineral content (BMC) by approximately one year, in both gender groups. This asynchronous increase in bone growth and BMC accrual leads to a "transient period of skeletal fragility", which explains in part the increase in childhood fractures during the peripubertal period (see below). Also, during this period gender differences in width of cylindrical long-bones are established. The increase in bone width that occurs through deposition of new bone at the periosteal surface is greater in boys than in girls, while the deposition of bone at the endocortical surface, which is driven by estrogens, is greater in girls than in boys. At the end of skeletal growth, males have a higher BMC than females, due to their larger skeleton. This largely arises due to longer pre-pubertal and pubertal period of growth in boys than in girls. Peak bone mass, defined as the maximum bone mass accrued at the end of skeletal maturity, is largely achieved by early adulthood, and is considered to be an important determinant of the risk of osteoporotic fractures that occur in later life.

The strength of a bone, in other words it is resistance to fracture, is related to its BMC as well its shape and size. Throughout life, bones adapt their strength parameters (size, shape and BMC) through processes of bone modeling and remodeling, in response to mechanical loading, which arises mainly from muscle contractions. This involves increase in the cross-sectional area, cortical thickness and BMC accrual in discrete local packets throughout the skeleton, through a balanced process of bone resorption and reformation. Resorption of old bone is accomplished by osteoclasts, with osteoblasts filling in the resorption cavity with healthy new bone.

ASSESSMENT OF BONE STRENGTH

Bone mineral content and bone mineral density (BMD), which are the quantifiable parameters related to bone strength, can be measured in vivo by bone densitometry techniques.

Dual-Energy X-ray Absorptiometry (DXA) is the most widely used bone densitometry technique, Areal BMD (see below) measured by DXA predicts vertebral and non-vertebral fractures in children. DXA technology is based upon scanning the whole body or a skeletal region of interest, e.g., the lumbar spine, with X-ray beams of two different photon energies, in a two dimensional mode. The absorption (attenuation) of these X-ray beams is dependent upon the thickness, composition and density of the soft tissue and bone in the scan path. The X-rays which traverse through the body are measured by sensitive detectors and the attenuation of the low and high-energy photons permits assessment of the BMC (with reference to a bone mineral calibration phantom) of the scanned skeletal site separately from the surrounding soft tissues. DXA is also an invaluable tool for the assessment of the subject's total and regional soft tissue composition—lean body mass and fat mass.

Dual-energy X-ray absorptiometry provides the measurement of the total amount of BMC (g) contained within the scanned skeletal region and the two-dimensional projected bone area (BA; cm^2). The ratio of BMC and BA, expressed in units of g/cm^2, is referred to as the "areal bone mineral density" (aBMD). This aBMD is not a measure of volumetric density (g/cm^3) because it does not provide information about bone thickness. As the aBMD is a two dimensional projection of a three dimensional structure, it is influenced by differences in bone size; a large bone with the same volumetric BMD as a smaller bone will have a greater measured aBMD. Thus, interpretation of aBMD is challenging in children due to age related changes in skeletal size. Short stature and pubertal delay in chronic illness makes interpretation even more complex.

It is crucially important that the standard deviation scores (Z-scores) for a child's aBMD are estimated from a local, ethnic and gender matched reference database. Such a reference database for Indian children is available for the General Electric Lunar DXA machine. In children, lumbar spine (L1to L4) and the whole body (less head, which contains 20–40% of BMC) are the preferred sites for evaluation of BMC and aBMD by DXA. The 2013 International Society for Clinical Densitometry (ISCD) Pediatric Official Position statement (*http://www.iscd.org/official-positions/2013-iscd-official-positions-pediatric*) recommendations for DXA assessment in children and adolescents are as follows:

1. The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone.
2. The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis, in the absence of local disease or high-energy trauma.
3. In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and aBMD Z-score ≤ –2.0.
4. A clinically significant fracture history is one or more of the following: (i) two or more long bone fractures by age 10 years; (ii) three or more long bone fractures at any age up to age 19 years.
5. A BMC/aBMD Z-score more than –2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.
6. In children with short stature or growth delay, lumbar spine and total body less head (TBLH) BMC and areal BMD results should be adjusted using either bone mineral apparent density (BMAD, a surrogate for volumetric BMD) or the height Z-score.
7. In patients with primary bone disease, or at risk for a secondary bone disease, a DXA should be performed when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture, and the DXA results will influence that management.

FRACTURES IN HEALTHY CHILDREN

Fractures in otherwise healthy children are common injuries; approximately a third of all boys and girls will sustain at least one fracture before 17 years of age. The incidence of childhood fractures peaks at ages 11–12 years in girls and 13–14 years in boys. As mentioned previously, the "transient period of skeletal fragility" has been proposed as the cause of the increase in fracture incidence in the peripubertal period. The most common fracture site is the distal forearm, followed by fingers, wrist and clavicle. The vast majority of fractures occur due to trauma arising from falls while running, playing games and sports.

There is no guideline for the management of fractures in an otherwise healthy child. General measures to improve bone health, such encouragement of weight-bearing physical activities, provision of a diet adequate in calcium and correction of vitamin D deficiency seem reasonable. In those with recurrent fractures it is important to search for primary and secondary causes of osteoporosis (see below). Treatment with bisphosphonates is not indicated in this population.

OSTEOPOROSIS

Osteoporosis is a condition characterized by reduced bone mass (BMC) and disruption of bone architecture leading to fragility fractures. A pragmatic definition of a fragility fracture is that occurring following minimal trauma, e.g., after a fall from standing height or less. Vertebral compression fractures often present with symptoms of back pain, kyphosis or loss of height. However, vertebral compression fractures may be completely asymptomatic. Furthermore, they can occur even when aBMD is with the normal limits. Hence, in 2013 ISCD Pediatric Position Statement, it is stated that the finding of one or more vertebral compression fractures is indicative of osteoporosis, in the absence of local disease or high-energy trauma.

Causes of osteoporosis in children can be classified as primary, due to an inherent bone disorder, or as secondary, caused by chronic disease and/or its treatment.

Primary Osteoporosis

Genetic conditions that affect the quantity and quality of bone matrix proteins or bone mineralization are associated fragility fractures. The most common condition in this category is osteogenesis imperfecta (OI).

Osteogenesis Imperfecta

(Also see Chapter 49.10 on Skeletal Dysplasias)

Osteogenesis imperfecta is a heterogeneous heritable connective tissue disorder characterized by skeletal fragility. It affects between 1 in 10 to 30,000 live born children. The majority (90%) of cases are caused by mutations in the *COL1A1* and *COL1A2* genes (OI types I to IV) that encode for the pro-alpha-1(I) and pro-alpha-2(I) chains of type I collagen, the major component of the bone matrix. Most of these forms of OI are inherited as autosomal dominant trait; however around 25% of children with OI are due to new germ-line mutations.

Osteogenesis imperfecta type V is caused by heterozygous mutation in the interferon-induced transmembrane protein 5 *(IFITM5)* gene. Patients with this form of OI, which accounts for ~ 5% cases, have a tendency to form hyperplastic callus after fractures. Radiographs show dense metaphyseal bands and calcification of the interosseous membrane.

Osteogenesis imperfecta type VI is caused by autosomal recessive mutation in the serpin peptidase inhibitor clade F *(SERPINF1)* gene, which results in a mineralization defect. Bone histology in patients with OI type VI show osteomalacia and a "fish-scale" pattern of bone lamellation.

Between 2 of 5 % of OI (Types VII to XI) are caused by mutations in recessive genes, which impair post-translational modification or folding of type I collagen. These include genes that result in alteration or deficiency of collagen prolyl 3-hydroxylation complex formation [Cartilage associated protein *(CRTAP)*, Leucine proline-enriched proteoglycan 1 *(LEPRE1)* and Peptidylprolyl isomerase B *(PPIB)* mutations], or absence/dysfunction of the collagen chaperones [Serpin peptidase inhibitor clade H member 1 *(SERPINH1)* and FK506 binding protein 10 *(FKBP10)* mutations].

Recently, other autosomal recessive mutations which are not directly related to collagen type I, such as BMP1 (Bone morphogenetic protein 1; OI Type XIII) and WNT1 (OI Type XV) genes have been shown to cause OI.

Clinical features of OI are extremely variable, ranging from stillbirth due to numerous fractures in utero to only a few fractures throughout life. The fracture rate in OI tends to decrease after the onset of puberty. Apart from history of recurrent fractures, subjects with OI may also exhibit some of the following features: blue or gray scleral color, fragile skin, easy bruising, hernias, yellow crumbly teeth, (*dentinogenesis imperfecta*), joint laxity, presenile deafness and short stature.

Management of OI requires a multidisciplinary approach, which has to be individualized depending on severity and degree of impairment. The pediatric orthopedic surgeon has an important role in treatment of fractures and in correcting limb deformities, often with the aid of "growing" intramedullary rods. Physiotherapists and occupational therapist play a crucial role in rehabilitation after fractures/elective surgery, and in providing appropriate mobility aids. Provision of appropriate vitamin D and calcium supplements is also important. Bisphosphonates are a group of drugs that inhibit osteoclastic bone resorption resulting is an increase in BMD and aBMD, improvement in bone strength and reduction in the risk of fragility fractures. Cyclical intravenous bisphosphonate (pamidronate or zoledronic acid) therapy has been shown to improve muscle strength mobility and decrease fracture incidence in children with severe and moderately severe types of OI.

Idiopathic Juvenile Osteoporosis

This a rare disorder in which a previously healthy boy or a girl presents in the pre-pubertal period with insidiously occurring vertebral fractures, sub-metaphyseal fragility fractures of long bones and muscle weakness. The condition usually resolves spontaneously or improves after the onset of puberty. The etiology of idiopathic juvenile osteoporosis (IJO) is unknown but heterozygous inactivating mutations in the gene encoding the low-density lipoprotein receptor-related protein 5 (LRP5) have been described in 10% of patients. There are anecdotal reports of improvement in symptoms and BMD following treatment with cyclical intravenous pamidronate.

Osteoporosis-pseudoglioma Syndrome

This is a rare autosomal recessive inherited condition characterized by fragility fractures of long bones and vertebrae, blindness and learning difficulties. It arises from homozygous inactivating mutations in the low-density lipoprotein receptor-related protein 5 *(LRP5)* gene.

Secondary Osteoporosis

Causes of secondary osteoporosis in childhood include reduced mobility, inflammation, hypogonadism, under-nutrition and treatment of underlying disorders with systemic glucocorticoids. In conditions such as anorexia nervosa, increase in endogenous glucocorticoids production also contributes to low aBMD and increased fracture risk. In many chronic childhood conditions, several of these factors act together to compromise the skeletal health.

Osteoporosis due to Reduced Mobility

Cerebral palsy and Duchenne muscular dystrophy (DMD) are associated with significant skeletal morbidity related to chronic immobilization. In these children, muscle weakness and habitual inability to participate in normal load bearing activities results in reduced periosteal bone expansion. This leads to development of slender long bones with thin cortices and low BMD, which have increased propensity to fracture.

Children with moderate to severe CP are at increased risk of sustaining fracture following minimal trauma. Such fractures predominantly occur in lower limb bones, and are associated with low BMD. Risk factors for fracture in this group include non-ambulatory status, anticonvulsant use, presence of joint contractures, immobilization after surgery and poor nutrition. Risk of fracture is also higher in those who have suffered previous fractures.

Duchenne muscular dystrophy is an X-linked recessive disorder due to mutations in the dystrophin gene, which leads to progressive muscle weakness, so that affected boys are wheelchair bound by early teen years. It is associated with low BMD and increased risk of long-bone fractures. Boys with DMD are often treated with systemic glucocorticoids to keep them mobile for a longer period. Unfortunately, glucocorticoids increase the fracture risk, both in long bones and vertebrae, which in turn accelerate the loss of ambulation in these boys.

Osteoporosis due to Inflammatory Disorders

In childhood conditions associated with chronic inflammation, such as juvenile idiopathic arthritis and Crohn's disease, there is increased production of pro-inflammatory cytokines such as interleukin (IL)–1 beta, IL-6 and tumor necrosis factor (TNF) alpha. These cytokines increase osteoclast differentiation and survival through increased activation of nuclear factor-k-B ligand (RANKL), resulting in increased osteoclastic bone resorption. Poor growth, delayed puberty, physical inactivity, under-nutrition and vitamin D deficiency also contribute to low BMD and increased fracture risk in children with chronic inflammatory disorders.

Osteoporosis due to Hypogonadism and Undernutrition

Primary hypogonadism caused by conditions such as Turner syndrome, and secondary hypogonadism associated with thalassemia major and any chronic illness adversely affect skeletal health. In anorexia nervosa self-imposed chronic nutritional deprivation, hypogonadotropic hypogonadism and hypercortisolemia contribute to low aBMD and increased fracture risk.

Glucocorticoid-induced Osteoporosis

Systemically administered glucocorticoids continue to be used as immune suppressants, e.g., after organ transplant, and to suppress chronic inflammation in certain childhood disorders, e.g., asthma, rheumatologic disorders and inflammatory bowel disease. Chronic glucocorticoid use results in low BMD and an increased risk for fragility fractures. The pathogenesis of glucocorticoid-induced osteoporosis is mutifactorial; glucocorticoids act on osteoblasts causing a reduction in bone formation and they increase bone resorption by stimulating osteoclastogenesis. They also inhibit calcium absorption from the gastrointestinal tract and decrease the renal tubular reabsorption of calcium. Glucocorticoid-induced myopathy also contributes to bone loss through reduced mechanical loading of the skeleton. Finally, glucocorticoids blunt the effects of sex steroids on bone.

Management of Secondary Osteoporosis

Unlike in adults, there are no clear guidelines for prevention and treatment of secondary osteoporosis in children. Clearly, optimal control of the underlying chronic illness is important, although the use of systemic glucocorticoids should be avoided where alternative treatments are available, for example monoclonal anti-TNF-α antibody, infliximab, for the treatment of Crohn's disease. It is reasonable to provide the daily recommended intake of calcium for the child's age, and 400 IU of vitamin D per day. Where possible, participation in weight-bearing activities should be encouraged. Secondary hypogonadism should be treated with appropriate hormone replacement therapy, under the supervision of a pediatric endocrinologist.

Systemically administered bisphosphonates have also been used to treat children with secondary osteoporosis. However, a Cochrane review of bisphosphonate therapy for children and adolescents with secondary osteoporosis concluded that there was insufficient information in the studies included within the review to inform whether bisphosphonates would improve BMD in children. The compassionate use of intravenous bisphosphonates for those with recurrent fragility fractures and/or bone pain may be justified. Such treatment should be undertaken by a pediatrician/ pediatric endocrinologist with expertise in assessment and management of pediatric bone disorders.

IN A NUTSHELL

1. The strength of a bone is related to the amount of bone mass (bone mineral content, BMC) contained within the periosteal envelope, as well its shape and size.
2. Bone mineral content and BMD, which are the quantifiable parameters related to bone strength, can be measured in vivo by Dual-Energy X-ray Absorptiometry (DXA). In children, lumbar spine and the whole body are the preferred sites for evaluation.
3. The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone. The presence of a vertebral crush fracture or clinically significant other fractures(s) is important for the diagnosis.
4. Osteoporosis in children can be classified as primary, due to an inherent bone disorder, or as secondary, caused by chronic disease and/or its treatment.
5. The most common primary condition of bone fragility is OI, the management of which requires a multidisciplinary team including the orthopedic surgeon, the physiotherapist and occupational therapist, nutritionist, and the pediatric endocrinologist for medical therapy.
6. Causes of secondary osteoporosis in childhood include reduced mobility, inflammation, hypogonadism, under-nutrition and treatment of underlying disorders with systemic glucocorticoids.

MORE ON THIS TOPIC

Bianchi ML, Leonard MB, Bechtold S, et al. Bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD Pediatric Official Positions. J Clin Densitom. 2014;17:281-94.

Khadilkar AV, Sanwalka NJ, Chiplonkar SA, et al. Normative data and percentile curves for Dual Energy X-ray Absorptiometry in healthy Indian girls and boys aged 5-17 years. Bone. 2011;4:810-9.

Leanne W, Mughal ZM, Bachrach LK. Osteoporosis in childhood and Adolescence. In: Marcus R, Feldman D, Dempster DW, et al. Osteoporosis. 4th ed. USA: Elsevier; 2013. pp.1037-72.

Chapter 44.29
Monogenic Obesity
Leena Priyambada

The prevalence of obesity has increased alarmingly over the past few decades. This increase has been mainly due to high calorie diet and lifestyle changes (see also Chapter 19.7). But obesity is a result of interaction between genetic factors and environmental factors. Twin and sibling studies have suggested that genetic factors can explain up to 50–90% of variance in body mass index (BMI). In contrast to this common garden-variety obesity, however, there exist rarer causes of obesity due to abnormalities of specific genes, also known as monogenic obesity. These genes play an important physiological role in the leptin-melanocortin system of energy balance as well as the development and function of the hypothalamus. Identification of these mutations has significantly helped unravel the role of the leptin-melanocortin system as well as the hypothalamus in the energy homeostasis of the body.

The classically recognized *syndromic obesity* like Bardet-Biedl, Prader-Willi, Alstrom, and others are due to genetic pleiotropy (when one gene influences multiple, seemingly unrelated phenotypic traits). **Box 1** lists some clinical clues that may help in suspecting endogenous obesity. Characteristic features of monogenic obesity/ obesity syndromes are briefly outlined in **Table 1**.

THE LEPTIN-MELANOCORTIN SYSTEM

The leptin-melanocortin system is a specific network of neurons, located in the hypothalamus that regulates long-term energy homeostasis in mammals. The information regarding the body's peripheral energy stores (adipocytes) is conveyed via the hormone leptin, and integrated in the hypothalamus. The effective output is a change in food intake behavior, and basal energy expenditure.

Leptin is a peptide hormone secreted by white adipose tissue in proportion to the body fat mass. In the arcuate nucleus of the hypothalamus (Arc) leptin binds to its receptors (LepR) activating the anorexigenic pro-opiomelanocortin (POMC) neurons and inhibiting the orexigenic agouti-related peptide (AgRP)/ neuropeptide-Y (NPY) neurons. These neurons further relay to the paraventricular nucleus (Pvn) of the hypothalamus which expresses melanocortin-4 receptors (MC4R) **(Fig. 1)**.

On activation of POMC neurons by leptin, α-melanocyte-stimulating hormone (α-MSH) is produced from POMC by prohormone convertase1/3 (PC1/3). α-MSH stimulates MC4R which relays a satiety signal and results in decreased food intake. On the other hand, AgRP competes with α-MSH to bind to MC4R and antagonizes it. Leptin inhibits these AgRP neurons. Together, both these pathways help in activation of MC4R and lead to satiety and a decrease in food intake. Any mutation in this pathway (namely leptin, LepR, POMC and PC1/3, and MC4R) resulting in deficiency or inactivation causes obesity.

BOX 1 Clues to suspect endogenous obesity

- History
  - Early onset severe obesity
  - Neonatal hypotonia and feeding problems
  - Developmental delay, learning disabilities, mental retardation
  - Visual complaints especially night-blindness, photodysphoria, complete blindness
  - Significant hyperphagia with food seeking behavior
  - Family history of syndromic obesity
- Examination
  - Characteristic facial dysmorphism
  - Digit abnormalities: polydactyly, syndactyly, brachydactyly, short stubby fingers, toes
  - Short stature
  - Delayed puberty
  - Pigmentary retinopathy
  - Morbid obesity
  - Deafness
  - Associated systemic/endocrine abnormalities, e.g., renal anomalies, congenital heart defects, pseudohypoparathyroidism.

Table 1 Characteristic features of monogenic obesity/obesity syndromes

Disease	Gene	Chromosome	Clinical features
Leptin deficiency	OB	7q32.1	Early-onset severe obesity, hyperphagia, hypogonadism, no short stature, low leptin levels
Leptin receptor deficiency	LEPR	1p31.3	Early-onset severe obesity, hyperphagia, hypogonadism, proportionately elevated leptin levels
Pro-opiomelanocortin (POMC) deficiency	POMC	2p23.3	Adrenal insufficiency, hyperphagia, red hair, fair skin
Melanocortin-4 receptor deficiency	MC4R	18q21.32	Early-onset obesity, hyperphagia, increased growth velocity, non-syndromic
Prohormone-convertase deficiency	PCSK1	5q15	Hyperphagia, obesity, mild hypocortisolism, diarrhea
Bardet-Biedl syndrome	BBS 1-18	Genetically heterogeneous	Retinitis pigmentosa, mental retardation, polydactyly, hypogonadism
Prader-Willi syndrome	NDN, SNRPN	15q11.2	Short stature, mental retardation, hypogonadism, almond-shaped eyes, small hands and feet
Albright hereditary osteodystrophy	GNAS	20q13.32	Short stature, round facies, ectopic soft tissue ossification, brachydactyly
Carpenter syndrome	RAB23, MEGF8	6p11.2 19q13.2	Acrocephaly, malformed ears with deafness, poly/syn/brachydactyly, growth retardation and mental retardation, hypogonadism
Cohen syndrome	COH1	8q22	Psychomotor retardation, microcephaly, hypotonia, joint laxity, retinochoroidal dystrophy
Alstrom syndrome	ALMS1	2p13.1	Cone dystrophy, short and stubby fingers, hearing loss, nephropathy, hyperinsulinemia
Börjeson-Forssman-Lehmann syndrome	PHF6	Xq26.2	Severe intellectual disability, epilepsy, hypogonadism, gynecomastia, large fleshy ear lobes
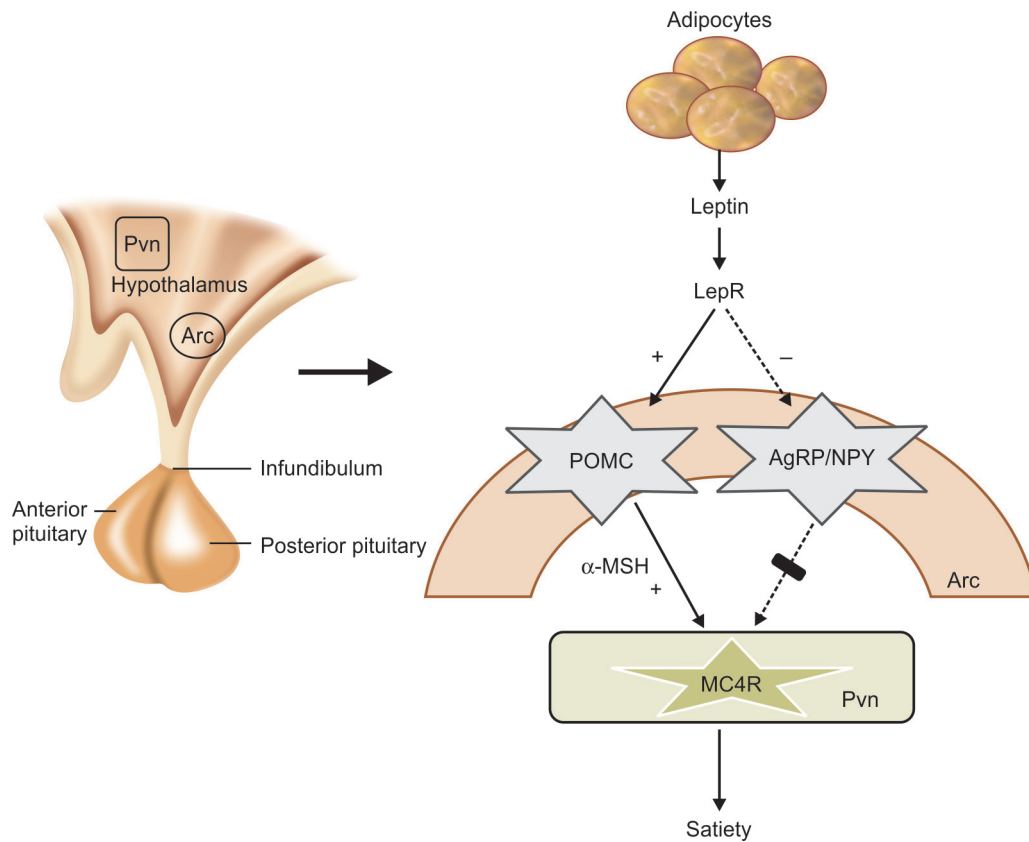
Figure 1 The leptin-melanocortin system: Leptin, secreted by the adipose tissue, binds to its receptors (LepR) present in the pro-opiomelanocortin (POMC)-expressing neurons and the agouti-related peptide (AgRP)/neuropeptide-Y (NPY)-expressing neurons in the arcuate (Arc) nucleus of the hypothalamus. Binding of leptin to LepR activates the POMC neurons and releases α-melanocyte-stimulating hormone (α-MSH). α-MSH stimulates melanocortin-4 receptors (MC4R) in the paraventricular (Pvn) nucleus causes decrease in food intake. Binding of leptin to LepR inhibits the orexigenicAgRP/NPY neurons which is an antagonist of MC4R, and hence also leads to decreased food intake

GHRELIN

Ghrelin is an orexigenic peptide secreted mainly from the stomach and the proximal small intestine. It stimulates appetite and promotes food intake. It acts as a growth hormone secretagogue. Plasma ghrelin levels are negatively corelated with body weight. Ghrelin mediates its action via NPY, AgRP neurons and inhibition of POMC neurons; as well as by vagal afferents. Mutations with ghrelin and ghrelin receptor associated with obesity are also reported, but not well established and will not be further discussed here.

OBESITY DUE TO MUTATIONS AFFECTING THE LEPTIN-MELANOCORTIN SYSTEM

Leptin Deficiency

Congenital leptin deficiency is a rare autosomal recessive disorder caused by mutation in the *ob* gene. This disorder is characterized by severe early-onset obesity, extremely low serum leptin level, and successful treatment with exogenous leptin. These individuals have normal birthweight, but develop severe hyperphagia in early infancy and become increasingly obese by 3–4 months. They weigh more than 20 kg by 1 year and more than 50 kg by 5 years of age. These patients may also have insulin resistance, hyperglycemia, hypogonadotropic hypogonadism and impaired hypothalamic-pituitary-thyroid axis. Linear growth is not stunted. Since leptin has a role in proliferation of CD4+ T-cells and release of cytokines from T-helper-1 cells, leptin-deficient patients have defective T-cell mediated immunity. Genetic analysis is important for diagnosis. Daily subcutaneous injections of recombinant human methionyl-leptin (R-metHuLeptin) results in impressive weight loss, reduction in fat mass, resumed pubertal progression, as well as improved thyroid and immune function.

Leptin Receptor Deficiency

Homozygous mutation in the LepR has clinical features similar to leptin deficiency with rapid weight gain starting early in infancy. At adolescence, their BMIs are 50–70 kg/m^2, their body fat greater than 65%, and without any pubertal changes. Serum leptin levels are elevated but in proportion to the body fat mass, and not excessively as one would expect from a receptor deficiency.

Pro-opiomelanocortin Deficiency

Pro-opiomelanocortin (POMC)-expressing neurons are located in the arcuate nucleus of hypothalamus, corticotropes and skin. After leptin signaling, POMC undergoes tissue-specific post-translational processing by prohormone convertase (PC) enzymes. PC1 produces ACTH in the corticotropes and PC2 produces melanocortins (α-, β-, γ-MSH) in the hypothalamus. MSH stimulates melanocortin-3 receptor (MC3R), MC4R and results in satiety. As ACTH is deficient, POMC mutations present in the newborn period with adrenal insufficiency and require glucocorticoid replacement. Hyperphagia and extreme obesity develop subsequently. Fair skin and red hair due to absence of MSH may be present. Heterozygous mutations predispose to obesity but do not have hypocortisolism.

Proprotein (Prohormone) Convertase 1/3 Deficiency

Prohormone convertases (PC) are tissue-specific endoproteases that cleave inactive hormone precursors like proTRH, proinsulin, proglucagon, proGHRH, POMC, proNPY into biologically active peptides. In the leptin-melanocortin system PC1/3 cleaves POMC into ACTH and MSH. PC1/3 deficiency is characterized by hyperphagia, obesity, mild hypocortisolism and diarrhea. This deficiency is extremely rare. Demonstrating a high proinsulin-to-insulin ratio after a glucose load gives a clue to PC1/3 deficiency.

Melanocortin-4 Receptor (MC4R) Deficiency

MC4R deficiency is the most common monogenic form of human obesity affecting 4–6% of severely obese populations. These mutations have autosomal dominant inheritance. There is severe obesity from early infancy with food seeking behavior, but they are otherwise non-syndromic with no peculiar abnormalities and attain normal puberty. These children have increased growth velocity in childhood.

OBESITY DUE TO MUTATIONS AFFECTING NEURODEVELOPMENT

SIM1, BDNF, NTRK2

SIM1, *BDNF*, and *NTRK2* have been shown to be important for development of the hypothalamus. *SIM1* is also postulated to function downstream of MC4R.

Individuals with *SIM1* mutation (chromosome 6q) have early-onset severe obesity, hyperphagia, increased linear growth, and are not associated with any developmental abnormalities, syndromic features, or endocrine dysfunction.

Brain-derived neurotropic factor *(BDNF)* and its receptor tropomyosin-related kinase B (TRKB) regulate the development and postnatal plasticity of hypothalamic neurons. They are also important for memory, behavior, and cognitive development. Deficits in these genes therefore, may present with impairment in these functions in addition to hyperphagia and severe obesity.

OBESITY SYNDROMES DUE TO GENETIC PLEIOTROPY

Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is mostly an autosomal recessive disorder characterized by obesity, pigmentary retinopathy, postaxial polydactyly, polycystic kidneys, hypogenitalism, and learning disabilities **(Fig. 2)**. There may be associated diabetes, hypertension, cardiomyopathy or Hirschsprung disease. Mutations in at least 18 different genes (*BBS1* to *BBS18*) have been documented. The pathogenesis is recently linked to primary cilium dysfunction. Laurence–Moon syndrome (LMS) as a distinct or the same clinical entity as BBS is not clearly established, though the initial LMS patient documented in literature had progressive neurological manifestations and spasticity.

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is due to absence of paternally-expressed genes at 15q11.2-q13 due to paternal deletion (65–75%), maternal uniparental disomy (20–30%), or an imprinting defect (1–3%). PWS is characterized by decreased fetal movements, severe hypotonia with poor suck and failure to thrive during infancy, followed by hyperphagia and early-childhood onset obesity **(Fig. 3)**. There is narrow bifrontal diameter, almond-shaped
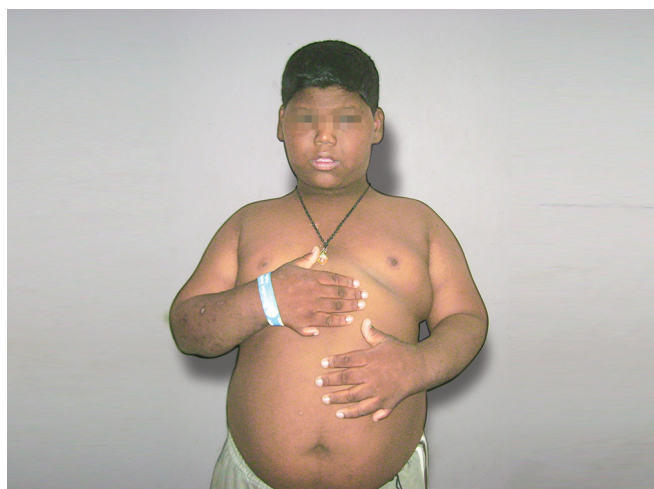
Figure 2 Bardet-Biedl syndrome

Figure 3 Prader-Willi syndrome

mild upslanted eyes, hypopigmentation, and small hands and feet. Short stature, developmental delay and hypogonadism are present. The mainstay of diagnosis is genetic testing; DNA based methylation testing, fluorescence in situ hybridization, or chromosomal microarray. Growth hormone (GH) replacement therapy provides improvement in growth, body composition, and physical attributes and is recommended apart from supportive management.

Alstrom Syndrome

Alstrom syndrome (ALMS) is an autosomal recessive disorder with childhood obesity, blindness and sensorineural hearing loss. They have distinctive facial features, like round face, deep-set eyes, thick ears, dental anomalies, hyperostosis frontalis interna, and short, stubby fingers with no polydactyly or syndactyly. The cone dystrophy leads to photodysphoria, night-blindness and complete blindness. Patients may also have associated hyperinsulinemia, hypertriglyceridemia, hypothyroidism, hypogonadism and dilated cardiomyopathy. There may be progressive pulmonary, hepatic, and/or renal dysfunction.

Albright Hereditary Osteodystrophy

The characteristic features of Albright hereditary osteodystrophy (AHO) phenotype are short stature, obesity, round facies, ectopic soft tissue ossification, brachydactyly affecting mainly the fourth and fifth digits **(Figs 4 to 6)**, and/or mental retardation.

Figure 4 Albright hereditary osteodystrophy

Figure 6 Dimpling of fist seen due to short fourth metacarpal in Albright hereditary osteodystrophy

Cohen Syndrome

Cohen syndrome is an autosomal recessive disorder largely seen in the Finnish population, characterized by psychomotor retardation, microcephaly, hypotonia and joint laxity, progressive retinochoroidal dystrophy, mid-childhood truncal obesity and intermittent neutropenia.

MANAGEMENT

Management of most of these disorders (apart from congenital leptin deficiency and partly Prader-Willi) is symptomatic and needs a multidisciplinary team approach. The general principles described in the management of exogenous obesity in Chapter 19.7 also apply to the monogenic and syndromic obesities.

Figure 5 Brachydactyly seen in a girl with AHO phenotype (PHP1a)

In pseudohypoparathyroidism (PHP)1a, AHO phenotype may be associated with hypocalcemia and hyperphosphatemia due to end organ resistance to parathyroid hormone (PTH). PHP1a is caused by loss of function of the Gs-alpha isoform of the *GNAS* gene on the maternal allele. Similar mutation in the paternal allele causes AHO phenotype without hormone resistance seen in pseudopseudohypoparathyroidism (PPHP).

Börjeson-Forssman-Lehmann syndrome

Börjeson-Forssman-Lehmann syndrome is an uncommon X-linked disorder characterized by moderate to severe intellectual disability, epilepsy, hypogonadism, late childhood obesity with marked gynecomastia. Typically present are large fleshy ear lobes, coarse facies and small genitalia. Females may be affected but with milder manifestations. This is caused by mutations in the zinc finger gene *PHF6*, which is speculated to play an important role in cell growth and proliferation.

Carpenter Syndrome

Carpenter syndrome is a subtype of acrocephalopolysyndactyly (ACPS) disorders. It is a rare autosomal recessive disorder with craniofacial dysmorphism like acrocephaly (tower-shaped skull), down-slanting eyes, low-set malformed ears with hearing loss. Abnormal digits (polydactyly/syndactyly/brachydactyly), obesity, congenital heart defects, umbilical hernia, small genitalia, visual problems, growth retardation and mental retardation are also present. It is due to mutations in the *RAB23* or *MEGF8* gene.

IN A NUTSHELL
1. The leptin-melanocortin system and the hypothalamus play an important role in the long-term energy homeostasis of the human body.
2. Satiety is associated with the activation of anorexigenic hormones/receptors leptin, POMC, MC4R, and inhibition of AgRp/NPY.
3. Short stature, facial dysmorphism, visual deficits, poly-/syn-/brachydactyly are important clues towards syndromic obesity.
4. A multidisciplinary approach is required for management of endogenous obesity.

MORE ON THIS TOPIC

Alemzadeh R, Rising R, Lifshitz F. Obesity in children. In: Lifshitz F. Pediatric Endocrinology. 5th ed. New York: Informa healthcare; 2007. pp. 1-36.

Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14:10-26.

Chandler KE, Kidd A, Al-Gazali L, et al. Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome. J Med Genet. 2003;40:233-41.

Gécz J, Turner G, Nelson J, Partington M. The Börjeson-Forssman-Lehman syndrome (BFLS, MIM #301900). Eur J Hum Genet. 2006;14:1233-7.

Levine MA. An update on the clinical and molecular characteristics of pseudohypoparathyroidism. Curr Opin Endocrinol Diabetes Obes. 2012;19: 443–51.

Marshall JD, Maffei P, Collin GB, Naggert JK. Alström syndrome: genetics and clinical overview. Curr Genomics. 2011;12:225-35.

M'hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of Bardet-Biedl syndrome. Mol Syndromol. 2014;5:51-6.

Ranadive SA, Vaisse C. Lessons from extreme human obesity: monogenic disorders. Endocrinol Metab Clin North Am. 2008;37:733-51.

Chapter 44.30
Hyperlipidemia
Nisha Bhavani

Lipoproteins are macromolecules, which are made-up of a hydrophobic core of triglycerides (TG), and cholesterol esters (CE) surrounded by hydrophilic phospholipids, unesterified cholesterol (UC) and apoproteins (apo). Lipoproteins are classified into chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL), which differ in their density, size and composition **(Table 1)**.

LIPOPROTEIN METABOLISM

The dietary lipids, mainly TG, are incorporated into chylomicrons which are absorbed through the lymphatic system into the circulation. When they reach muscle and peripheral tissues they are metabolized by lipoprotein lipase (LPL) enzyme for which apolipoprotein C-II (apo C-II) is required as a cofactor. The remnant chylomicrons are then transported into the liver to be internalized by LDL receptor (LDL-R) by interaction with apo E. The liver synthesizes VLDL rich in TG and cholesterol which undergo the same metabolism like chylomicrons by LPL in presence of apo C-II and are returned to the liver as VLDL remnants called IDL. Part of IDL is internalized by LDL-R through apoE in liver and the remaining is acted upon by hepatic lipase to produce LDL. This LDL is the main circulating cholesterol in the body. It is metabolized in the liver by LDL-R through apo B-100 or is taken up by steroid requiring cells. The excess LDL is taken into the subintimal space where it is oxidized and initiates the process of atherosclerosis. The cholesterol secreted by liver, intestine and peripheral tissues is also incorporated into nascent HDL, which gets mature by esterification of the cholesterol by *lecithin-cholesterol acyltransferase* (LCAT) enzyme. These HDL exchange its CE with TG of VLDL and IDL which in turn gets metabolized by LDL-R. HDL is directly metabolized by scavenger receptors present in liver. Thus, HDL is involved in reverse cholesterol transport of cholesterol. The cholesterol ultimately gets excreted from the liver through the bile and then through the intestine.

DISORDERS OF LIPOPROTEIN METABOLISM

The Frederickson classification divides disorders of lipoprotein metabolism into five types based on the lipoproteins which are elevated **(Table 2)**. Many molecular defects and acquired conditions can contribute to each of these hyperlipoproteinemias (HLP). Types IIA, IIB and IV are common in children; Type 1 and V are rare and Type III is almost always seen in adults. Frederickson's classification is easy to understand, but less commonly used after the advent of molecular diagnostic tests.

Disorders Associated with Hypertriglyceridemia

Familial Chylomicronemia Syndrome

Previously called type I HLP, familial chylomicronemia syndrome (FCS) is characterized by elevated chylomicrons. FCS is due to LPL deficiency or apoC-II deficiency both of which are autosomal recessive conditions. Fasting plasma, when left alone at 4°C for few hours, will show cloudy supernatant indicating chylomicrons. The fasting triglyceride levels are more than 1000 mg/dL. Children usually present with recurrent episodes of pancreatitis. Retinal examination will show white to yellow retinal vessels called lipemia retinalis. The chylomicrons not cleared by the tissues due to defective LPL or apoC-II will be taken up by endothelial cells resulting in hepatosplenomegaly and eruptive xanthomas. Eruptive xanthomas are small cutaneous itchy painless papules seen mainly in the back, buttocks and extensor aspects **(Fig. 1)**. These children are generally not at risk of premature cardiovascular disease (CVD).

The management of type I HLP is by dietary fat restriction to less than 15% of daily caloric intake. Medium chain triglycerides (MCT) are not made into chylomicrons and are directly absorbed into portal circulation. MCT oil can therefore be used in the diet. Coconut oil is a rich source of MCT. Restriction of fat leads to fat soluble vitamin deficiencies which should be supplemented in the diet. Medications which have been used include omega-3 fatty acids from fish oils. Some patients especially those with apoC-II deficiency will respond to fresh frozen plasma infusions. In extreme situations plasmapheresis has also been used to remove circulating chylomicrons.

Familial Hypertriglyceridemia Syndrome

Familial hypertriglyceridemia syndrome **(**FHTG) can present as isolated elevation of VLDL (type IV) or both VLDL and chylomicrons (type V). Type IV is more common than type V in the pediatric population. The TG levels are in the range of 250–1000 mg/dL with normal cholesterol and low HDL levels, with family members having similar lipid profiles. Familial hypertriglyceridemia should be differentiated from the more sinister familial combined hyperlipidemia (FCH) and familial dysbetalipoproteinemia (FDBL) both of which are associated with high risk of CVD. High fat and carbohydrate diet and alcohol intake worsens the condition. Lifestyle modification is the major therapeutic intervention to reduce the risk of pancreatitis with pharmacological agents like fish oil and statins reserved as second line agents.

Disorders Associated with Hypercholesterolemia

Familial Hypercholesterolemia

Familial hypercholesterolemia **(**FH) is mainly due to defective LDL-R and is the older type IIA HLP. They are inherited in an autosomal dominant fashion and can be either homozygous or heterozygous. Those who are homozygous usually present in childhood with tendon xanthomas in the extremities and arcus

Table 1 Lipoproteins and their characteristics

Lipoproteins	Density (g/mL)	Size (nm)	Mobility	Apolipoproteins	Lipid
Chylomicrons	0.93	75–1200	Origin	Apo B 48, E, C	TG
VLDL	0.93–1.006	30–80	Pre-β	Apo B 100, E, C	TG
IDL	1.006–1.019	25–35	Slow Pre-β	Apo B 100, C, E	TG, UC
LDL	1.019–1.063	18–25	β	Apo B-100	UC
HDL	1.063–1.210	5–12	α	Apo A1, C, E	CE

Abbreviations: TG triglycerides; CE, cholesterol esters; UC, unesterified cholesterol; Apo, apolipoproteins; CM, chylomicrons; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins.

Table 2 Classification of Hyperlipidemia

Clinical features	Type I	Type IIA	Type IIB	Type III	Type IV	Type V
LP	CM	LDL	LDL, VLDL	IDL, CM remnants	VLDL	CM, VLDL
TG	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
TC	↑	↑↑↑	↑↑	↑↑	N	↑↑
LDL	↓	↑↑↑	↑↑	↓	↓	↓
HDL	↓	↓↓	↓↓	N	↓↓	↓↓↓
Plasma	Lipemic	Clear	Clear	Turbid	Turbid	Lipemic
Xanthomas	Eruptive	Tendon	No	Palmar, tuboeruptive	No	Eruptive
Pancreatitis	+++	–	–	–	–	+++
CAD	–	+++	+++	+++	+/–	+/–
Defect	LPL or apo C-II deficiency	LDL-R or apo B-100 deficiency	–	Apo E defect	–	–
Synonym	FC	FH	FCH	FDBL	FHTG	FHTG

Abbreviations: FC, familial chylomicronemia; FH, familial hypercholesterolemia; FCH, familial combined hyperlipidemia; FDBL, familial dysbetalipoproteinemia; FHTG, familial hypertriglyceridemia; CAD, coronary artery disease LP, lipoprotein; CM, chylomicron; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; IDL, intermediate density lipoproteins; TG, triglyceride, TC, total cholesterol; LPL, lipoprotein lipase; LDL-R, LDL receptor; apoC-II, apolipoprotein C-II; apoE, apolipoprotein E.

Figure 1 Eruptive xanthomas on the dorsum of hands in a child with familial chylomicronemia syndrome

senilis. Total cholesterol levels are more than 500–1000 mg/dL. Homozygous FH patients develop accelerated atherosclerosis at a very early age which is manifested as either aortic valve stenosis or coronary artery disease (CAD) often before puberty. Peripheral occlusive vascular disease (POVD) occurs later in life. If left untreated, homozygous patients die within the second decade. Diagnosis is suggested by a positive family history of premature CAD and or hypercholesterolemia wherein more than 50% of the first degree relatives are affected. Treatment with pharmacological agents is not uniformly successful in homozygous FH. They may require LDL apheresis and/or liver transplantation.

Heterozygous FH is extremely common (1 in 500 incidence) and presents similar to homozygous FH, but at a much later age usually in the late second decade with LDL levels varying form 200–400 mg/dL. Any child with a high cholesterol level needs an extensive family screening for this condition, since early treatment can markedly lower the incidence of adult CAD. They will respond to treatment with one or more cholesterol lowering drugs; only a few require LDL apheresis.

Defects in apoB-100 which is needed for the association of LDL with LDL-R can also lead to a phenotype similar to FH, but is much less severe than FH.

Disorders with both Hypercholesterolemia and Hypertriglyceridemia

Familial Combined Hyperlipidemia (FCH)
This is the old type IIB HLP characterized by excess of apoB containing lipoproteins, but its exact molecular pathogenesis is not known. They have a mixed hyperlipidemia with moderate elevations of either triglycerides in VLDL or cholesterol in LDL or both. Inherited as an autosomal dominant condition they often have other metabolic risk factors like obesity, insulin resistance, and systemic hypertension. Tendon xanthomas are absent. They are at significant risk of premature CAD. The TG vary form 200–800 mg/dL and TC varies form 200–400 mg/dL with a concomitant low HDL level. They are managed by intensive lifestyle modification and cholesterol lowering medications.

Familial Dysbetalipoproteinemia
This seldom occurs in children and is the old type III HLP. It is often called the broadband disease or remnant disease. This is due to genetic variations in apoE, those who are homozygous for the E2 allele has low affinity of apoE for LDL receptor and hence cannot clear chylomicron and IDL from the circulation. Patients usually present in adulthood with combined hyperlipidemia, tuboeruptive and palmar xanthomas and premature CAD and POVD. Familial dysbetalipoproteinemia (FDBL) is treated with aggressive lifestyle modifications and pharmacological agents.

SECONDARY CAUSES OF DYSLIPIDEMIA

Perhaps the most common cause of dyslipidemia seen in children in the present day world is secondary to lifestyle factors like unhealthy eating habits with high fat and simple carbohydrate diet and sedentary lifestyle leading to overweight or obesity and insulin resistance. This will lead to increased delivery of free fatty acids to the liver which are converted to TG and secreted as VLDL. The HDL levels will be low due to decreased lipolysis. Multiple gene defects may contribute to individual variation. The classic dyslipidemia

pattern observed in obesity and metabolic syndrome is thus high TG with low HDL. LDL is usually not elevated in insulin resistance unless it is associated with another lipoprotein abnormality or diabetic nephropathy. The same pattern of dyslipidemia is usually observed in diabetes in children. Another common cause of hyperlipidemia in children is nephrotic syndrome where there are high TG and cholesterol levels due to increased production as well as decreased clearance of lipoproteins. Hypothyroidism needs to be ruled out in all cases of hyperlipidemia. Other causes of hyperlipidemia include liver diseases producing cholestasis, lipodystrophy, alcohol abuse and medications like estrogen, glucocorticoids, thiazides, cyclosporine, etc.

SCREENING AND DIAGNOSIS

The latest guidelines issued by the National Heart Blood and Lung Institute (NHBLI) in 2011 recommend combining universal and selective screening for pediatric dyslipidemia. Universal screening for dyslipidemia is recommended for all children at two different points of time—first screening between 9 and 11 years of age and a second screening between 17 and 21 years of age. In addition to universal screening, the NHBLI also recommends selective screening outside of the age group of universal screening in those at high-risk of developing cardiovascular disease. This type of selective screening can begin as early as 2 years of age and include those with positive family history of premature coronary artery disease or other high risk factor associated with CVD like (1) diabetes mellitus or familial hypercholesterolemia or chronic kidney disease or nephrotic syndrome or post-transplant or Kawasaki disease or chronic inflammatory disease or HIV infection; (2) significant tobacco exposure; (3) systemic hypertension; (4) BMI more than 95th centile between 2 and 8 years of age and BMI more than 85th centile in older children; and (5) parent with dyslipidemia.

The screening tests recommended for selective screening is fasting lipid profile after a 12-hour overnight fast on two occasions for at least 2 weeks and not more than 12 weeks apart and that for universal screening is a nonfasting non-HDL cholesterol (total cholesterol—HDL cholesterol). Those with abnormal nonfasting non-HDL levels more than 145 mg/dL should do scheduled fasting lipid profile twice as in selective screening to establish the abnormality. The average of the two tests is taken to make decisions on starting therapy for pediatric dyslipidemia.

The cut off levels for plasma lipids in children and adolescents depending on 75th and 95th centile classified as borderline high and high, respectively are given in **Table 3**. More conservative guidelines recommended by American Acadeny of Pediatrics (AAP) in 2008 and National Cholesterol Education Program (NCEP) in 2001 recommends screening with fasting lipid profile of only high-risk children above 2 years of age (as specified in the selective screening of NHBLI above). In a resource, limited setting in India, this may be a more practical approach rather than universal screening.

Table 3 Normal levels of lipids in children

Category	Acceptable	Borderline high	High
TC *	< 170	170–199	> 200
LDL	< 110	110–129	> 130
Non-HDL	< 120	120–144	> 145
TG			
0–9 years	< 75	75–99	> 100
10–19 years	< 90	90–129	> 130
HDL	> 45	40–45	< 40 (low)

* All values in mg/dL
Abbreviations: TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein.

TREATMENT

All children with abnormal lipid levels should be prescribed lifestyle changes which include diet modification for a period of 3 months. This includes reduction of fat to 30% of daily calories, avoiding trans fat, reducing saturated fat to less than 10% of total daily calories, limiting sweetened beverages, limiting cholesterol intake, increasing polyunsaturated fatty acid intake and taking low fat milk and high dietary fiber. Further, intensified diet restriction and addition of plant sterols, water-soluble fiber and fish oils may be considered in the next 3 months.

Regular physical activity, reducing screen time, and engaging in regular household activities like sweeping, cleaning, etc., are important adjuvants to diet in reducing lipid levels and maintaining ideal body weight. If at the end of 6 months of intensive lifestyle changes, the goal of treatment is not met, pharmacological treatment is recommended. Indications for drug therapy are as follows:

- LDL > 190 mg/dL with no risk factors
- LDL > 160 mg/dL with any one risk factor
- LDL > 130 mg/dL in diabetes.
- Average TG > 500 mg/dL or a single TG > 1000 mg/dL.

Statins are HMG CoA reductase inhibitors which are approved for use in children above 10 years of age for lowering LDL levels. Commonly used statins in India are simvastatin and atorvastatin both of which are started at a dose of 10 mg/day. Rare side effects which can occur with statins are myopathy and hepatic enzyme elevation. Bile acid sequestrants were the first agents to be approved for reduction of LDL in children, but adherence may be a problem because of significant gastrointestinal discomfort. The cholesterol absorption inhibitor ezetimibe may also be used with modest cholesterol lowering efficacy in children. The pharmacological treatment of hypertriglyceridemia in children is extrapolated from adults and includes fish oils and statins. Fibrates have not been very well studied.

IN A NUTSHELL

1. Lipids form important components of cellular architecture and substrate for metabolic processes. Lipoproteins are involved in the transport and metabolism of lipids.
2. Hyperlipidemia occurring secondary to metabolic conditions such as diabetes mellitus, nephrotic syndrome and hypo-thyroidism are commonly encountered.
3. Primary hyperlipidemias are rare, but have important implications for serious consequences such as acute pancreatitis or premature coronary artery disease.
4. Prevention and treatment involve dietary modifications, pharmacological therapy and family screening.

MORE ON THIS TOPIC

Braamskamp MJ, Hutten BA, Wiegman A, Kastelein JJ. Management of hypercholesterolemia in children. Paediatr Drugs. 2014;16:105-14.

Chauhan A, Paunikar P. Update on pediatric hyperlipidemia. Curr Opin Pediatr. 2014;26:252-8.

Daniels SR. Management of hyperlipidemia in pediatrics. Curr Opin Cardiol. 2012;27:92-7.

de Ferranti SD. Childhood cholesterol disorders: the iceberg base or nondisease? Med Clin North Am. 2012;96:141-54.

Lamaida N, Capuano E, Pinto L, Capuano E, et al. The safety of statins in children. Acta Paediatr.2013;102:857-62.

Langslet G, Ose L. Screening methods in the diagnosis and assessment of children and adolescents with familial hypercholesterolemia. Expert Rev Cardiovasc Ther. 2013;11:1061-6.

McCrindle BW. Familial hypercholesterolemia in children and adolescents. Curr Opin Lipidol. 2012;23:525-31.

Stock J. New EAS Consensus Statement on FH: improving the care of FH patients. Atherosclerosis. 2013;231:69-71.

Chapter 44.31
Endocrine Consequences of Thalassemia Major

Archana Dayal Arya

Beta-thalassemia is a chronic blood disorder characterized by decreased production of the β globin chain and excess accumulation of the other globin chains. The homozygous state is associated with severe anemia, requiring regular blood transfusions to maintain normal hemoglobin. Hypertransfusion and increased absorption of iron due to ineffective erythropoiesis lead to an excess of iron in the body. Chelation of excess iron is very important to prevent damage to the various organs. The common drugs used for chelation are desferrioxamine (DFX), deferiprone and deferasirox. Poor chelation leads to excess iron deposition in organs with high levels of transferrin receptors such as the liver, heart and especially the endocrine glands. The anterior pituitary gland is particularly sensitive to free radicals induced oxidative stress, resulting in hypogonadism and short stature. Other endocrine organs plagued by iron deposition secondary to multiple transfusions include the pancreas, thyroid, and parathyroid glands leading to diabetes mellitus (DM), acquired hypothyroidism and hypoparathyroidism respectively **(Table 1)**. Despite good chelation therapy begun early in life, problems such as delayed sexual maturation, osteoporosis and impaired fertility may persist.

Bone marrow transplant (BMT) in children with thalassemia results in transfusion free survival, but effects of iron overload and the drugs used for conditioning prior to BMT may affect pubertal development and fertility. BMT done at a younger age reduces the risk of endocrine and other complications. Improvement in growth has been observed in these children post-transplant but gonadal failure is reported, especially in girls. Hence, they must be screened regularly for complications.

SHORT STATURE IN THALASSEMIA MAJOR

Short stature is one of the most common endocrine disorders seen in children with thalassemia and is prevalent amongst the poorly and the well-chelated children with thalassemia. About 30–40% children with thalassemia are reported to have short stature, even in the developed countries. These children usually have normal growth till the age of 8–9 years, followed by a decrease in the growth velocity during the peripubertal period. Delayed puberty and a blunted pubertal growth spurt usually result in a short final height.

Spinal growth in children with thalassemia is particularly impaired, resulting in short sitting height. The subischial leg length is less affected. Truncal shortening can be observed prior to puberty suggesting that it is not entirely due to delayed puberty, although it can worsen the disproportion.

The multiple factors that may contribute to short stature in thalassemia are listed in **Table 2**. In developing countries like India, short stature is more likely due to chronic anemia and iron overload, whereas in developed countries it is more likely due to DFX toxicity. Some of these are discussed in detail below:

Growth Hormone (GH)-Insulin-like Growth Factors (IGF) Axis

In addition to GH deficiency, which may occur in 20–60% in different studies, disorders of the GH-IGF-1 axis may also be present due to hypothalamic growth hormone releasing hormone (GHRH) deficiency, defective IGF synthesis in the liver because of siderosis and poor nutrition or neurosecretory dysfunction leading to growth hormone deficiency. The criteria for diagnosing GH deficiency are the same as in other children.

Desferrioxamine Toxicity

Short stature and skeletal dysplasia can be induced by use of excessive doses of DFX. The exact pathogenesis of DFX toxicity is not known but it is possibly due to (a) chelation of trace elements (zinc, copper), which play an important role in growth; or (b) inhibition of cellular proliferation. DFX may inhibit DNA synthesis, fibroblast proliferation and collagen formation and decreases the activity of alkaline phosphatase. DFX toxicity results in a skeletal dysplasia, characterized by metaphyseal widening of long bones, platyspondylosis of the vertebral bodies, slipped femoral head, genu valgum and a slowing of growth velocity.

Management of Short Stature in Thalassemia

Measurement of sitting height in addition to other routine measurements should be done. Investigations should include zinc levels and a skeletal survey. Mean pretransfusion hemoglobin should be kept above 9 g/dL to ensure normal growth. Correction of malnutrition and giving a high calorie diet may increase the weight and IGF-1 level. This may improve growth and the hypermetabolic state and reduce the risk of osteoporosis. *Folate deficiency* may occur in irregularly transfused or malnourished children who may be given 1–2 mg of folic acid daily or 5 mg weekly. Routine supplementation is not necessary in regularly transfused patients. *Zinc deficiency* can be present due to the effect of the chelating agents, DFX and deferiprone. Plasma zinc estimation helps in reaching a diagnosis. Oral zinc sulfate 200–220 mg should be given daily to patients with mild deficiency and the dose should be doubled or tripled in moderate to severe deficiency. If the blood consumption exceeds 200 mL/kg body weight, splenectomy should be considered.

Growth hormone insufficiency is treated with daily subcutaneous injections of recombinant human growth hormone. GH resistance may be overcome with supraphysiologic doses of GH and improvement in growth velocity has been reported in a number of studies. Data on final height with GH treatment is insufficient at present. Since recombinant human growth hormone also affects the glucose metabolism, which may be compromised in thalassemic children, it should be used judiciously under the supervision of an experienced pediatric endocrinologist.

Table 1 Endocrine complications of thalassemia major

• Short stature
• Hypogonadism including delayed and arrested puberty
• Hypoparathyroidism
• Hypothyroidism
• Diabetes mellitus
• Osteopenia/osteoporosis

Table 2 Causes of short stature in thalassemia

• Chronic anemia
• Nutritional deficiencies (deficiency of folic acid, zinc, etc.)
• Hypersplenism
• Endocrine disorders: Hypothyroidism, delayed puberty/hypogonadism, growth hormone insufficiency/resistance/disorders of GH-IGF-1 axis
• Desferrioxamine toxicity

Abbreviation: GH-IGF-1, growth hormone-insulin like growth factor-1.

Desferrioxamine toxicity The dose of DFX should be reduced to 20–25 mg/kg body weight, if the serum ferritin is below 1000 ng/mL to treat and prevent toxicity. In children with hypersensitivity to normal doses of DFX, treatment may have to be discontinued for variable periods of time or replaced by another chelating agent. Oral zinc supplements should be given and surgery may be required in severe cases for correction of the skeletal deformities.

HYPOGONADISM, DELAYED AND ARRESTED PUBERTY

Delayed sexual maturation or puberty, arrested puberty and hypogonadism are common problems encountered by patients with thalassemia. They are more likely to occur in the poorly chelated children. Delayed puberty may be constitutional (transient, commensurate with delayed bone age) or due to hypogonadism, which is usually due to iron deposits in the anterior pituitary gland causing hypogonadotropic hypogonadism. Puberty may also be arrested any time after onset. Girls may present with primary or secondary amenorrhea. Delayed puberty results in short stature, truncal shortening and worsening of the bone mineral density, since sex steroids are also responsible for bone mineralization. The pituitary gonadotropes are very sensitive to iron deposition. Occasionally, iron deposit may be present in the testes and in the ovaries after the age of 25 years. Fertility and pregnancy in thalassemic women is possible since ovulation is normal after stimulation.

Management

Delayed puberty must be treated at the appropriate time so that these children can have normal growth, sexual development and bone mass. Doses of replacement hormone should be escalated gradually so that growth potential is not hampered.

HYPOPARATHYROIDISM

Hypoparathyroidism usually occurs due to hemosiderosis of the parathyroid glands. Suppression of parathyroid secretion induced by bone resorption due to increased hematopoiesis secondary to chronic anemia has also been suggested as a cause of impaired secretion of parathyroid hormone (PTH). Symptoms may not be present initially in these children unless hypocalcemia is severe or there is a rapid drop in the serum calcium level. Tetany or seizures may occur typically in this situation. Extensive intracranial calcification has been reported in thalassemics with hypoparathyroidism. Hence, it is important to screen thalassemic children regularly for hypoparathyroidism. Oral administration of calcitriol and calcium normalizes the calcium and phosphorus.

HYPOTHYROIDISM

Hypothyroidism usually occurs in poorly chelated patients due to excess iron deposition in the thyroid gland, although some studies have reported central (secondary) hypothyroidism.

Replacement therapy is given with *l*-thyroxine and levels of both T4 and TSH should be monitored regularly for adjusting the dose of thyroxine.

DIABETES MELLITUS AND ABNORMALITIES OF GLUCOSE METABOLISM

The etiology for diabetes mellitus (DM) is multifactorial including genetic predisposition (higher in Indian population), insulin resistance, liver dysfunction secondary to iron overload and viral hepatitis, insulin deficiency and beta cell destruction secondary to iron overload. Patients usually present with impaired glucose tolerance (IGT) mostly due to insulin resistance and subsequently develop insulin deficiency. Routine screening with glucose tolerance test should be done from 10 years of age. In thalassemics with IGT, intensive chelation with DFX and deferiprone may delay or prevent the onset of DM. Dietary modification and weight loss in the obese should also be recommended. Metformin offers some protection against diabetes and stimulates osteoblast differentiation, helping in bone formation. In thalassemic children with diabetes, ketoacidosis is seldom a presenting symptom. Insulin therapy is considered in the stage of insulin deficiency, the insulin regime being similar to that in other children with insulin-dependent diabetes mellitus (IDDM). The role of oral hypoglycemics for management of DM in these children is not well established.

Metabolic control in these patients may be difficult to achieve. Fructosamine testing may be used as a target for metabolic control rather than HbA_{1c} since it relies on a normal structure of hemoglobin. Screening for complications secondary to diabetes should be done regularly as in other insulin deficient diabetic children.

BONE DISEASES: OSTEOPENIA AND OSTEOPOROSIS

Osteopenia and osteoporosis are the most common bone complications of thalassemia. The reported frequency of osteoporosis in well-treated thalassemia patients varies from 13.6% to 50% with an additional 45% affected by osteopenia. Hypogonadism and abnormality in the GH axis are the major endocrine factors responsible for this condition. Genetic factors, diabetes, hypothyroidism, vitamin D deficiency, zinc deficiency, ineffective hemopoiesis leading to marrow expansion, effect of excess iron on osteoblasts, and chronic liver disease are also suspected to contribute to osteoporosis in thalassemia.

The definition of osteoporosis for children differs from that of adults. It includes a low bone mineral density (BMD) as well as a history of pathological fractures. Low BMD is defined as a Z (standard deviation) score below –2 SD. Dual energy X-ray absorptiometry (DEXA) scan is the method of choice to assess BMD. Clinical presentation includes backaches, bone pain and fractures. In case of severe backache, MRI spine should be done to rule out intervertebral disc degeneration.

Prevention of osteoporosis should be the main goal **(Table 3)**. Bisphosphonates that prevent osteoclastic resorption

Table 3 Prevention of osteoporosis in thalassemia major

• Adequate calcium and vitamin D intake; 800 units of vitamin D and 500–1000 mg of calcium as daily supplement from 12 years onward; determination of urinary calcium excretion before calcium supplementation is recommended
• A high calorie diet to compensate for the hypermetabolic state of thalassemia major patients increases body weight and IGF-1 levels with potential beneficial effect on bone accretion and consequentially on peak bone mass
• Avoidance of alcohol consumption, coffee and smoking in adolescents
• Regular exercise; minimum 30 min at least 3–4 times a week
• Timely intervention in delayed puberty
• Early and appropriate management of hypoparathyroidism, hypothyroidism, and diabetes mellitus
• Preventing iron overload
• Adequate blood transfusion to prevent medullary expansion

may be considered for children who have had minimal trauma fractures. Calcitonin, an osteoclast inhibitor has been used to relieve bone pain and prevent fractures in thalassemia patients.

ADRENAL INSUFFICIENCY

Adrenal insufficiency (AI) can occur due to excess iron deposition either in the pituitary gland leading to secondary adrenal insufficiency or in the adrenal gland (primary adrenal insufficiency). Prevalence of biochemical insufficiency has been reported in 0–45% cases. Low adrenal androgen levels are fairly common in thalassemia leading to delayed appearance of pubic, axillary and facial hair. Serum cortisol level should be measured at 8 am to screen for adrenal insufficiency. If low levels are present, ACTH stimulation test (described in Chapter 44.16) should be performed. Symptoms of AI are uncommon and often missed since fatigue, muscle weakness, etc., are common symptoms in thalassemics. Adrenal crisis is very rare. Replacement therapy with glucocorticoids should be given in those with deficiency and only during stress in those with subclinical insufficiency.

BONE MARROW TRANSPLANT

Bone marrow transplant (BMT) in children with thalassemia results in transfusion free survival, but effects of iron overload and the drugs used for conditioning prior to BMT may affect pubertal development and fertility. BMT done at a younger age reduces the risk of endocrine and other complications. Improvement in growth has been observed in young children post-transplant but gonadal failure is reported, especially in girls. Hence, these children must be screened regularly for endocrine complications. Sperm banking and cryopreservation of ovarian cortex should be considered in adolescents with normal spermatogenesis/ovulation prior to transplant.

GUIDELINES FOR SCREENING

The current management of thalassemia includes regular transfusions and chelation therapy. Unfortunately, chelation is suboptimal in most Indian patients due to economic reasons and ignorance; hence endocrine complications are frequent and tend to occur at a young age. Clinical manifestations may be subtle, hence regular monitoring of growth, pubertal staging, and screening for endocrine complications should be a part of management of thalassemic children. Guidelines for screening for endocrine complications recommended by The International Network on Endocrine Complications in Thalassemia (I-CET) are given in **Table 4**. Early screening reduces morbidity and would result in better quality of life for these children.

Table 4 Suggested screening for endocrine consequences in children with thalassemia

- Growth monitoring with sitting height measurement annually
- Pubertal assessment from 8 years onward
- Annual measurement of LH, FSH and serum testosterone in males who have completed puberty
- Calcium and vitamin D levels annually
- Zinc status should be assessed annually in all children and adults with thalassemia. Those with serum plasma zinc less than 70 μg/dL should be treated with zinc supplementation
- Screening for impaired glucose tolerance: at least once every 2 years starting from 10 years of age, up to 16 years, and then once every year
- Thyroid functions annually after 9 years of age (sooner if symptoms of hypothyroidism appear)
- DEXA scan from 10–12 years of age, every 2 years for BMD
- Serum cortisol at 8 am for adrenal insufficiency

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMD, bone mineral density; DEXA, Dual energy X-ray absorptiometry.

MORE ON THIS TOPIC

De Sanctis V. Growth and puberty and its management in thalassaemia. Horm Res .2002;58(Suppl 1):72-9.

De Sanctis V, Soliman AT, Elsedfy H, et al. Growth and endocrine disorders in thalassemia: The International network on endocrine complications in thalassemia (I-CET) position statement and guidelines. Indian J Endocrinol Metab. 2013;17:8-18.

De Sanctis V, Vullo C, Bagni B, Chiccoli L. Hypoparathyroidism in beta-thalassemia major. Clinical and laboratory observations in 24 patients. Acta Haematol. 1992;88:105-8.

El Kholy M, Elsedfy H, Soliman A, et al. Towards an optimization of the management of endocrine complications of thalassemia. J Pediatr Endocr Metab. 2014;27:801-5.

Low LC. Growth of children with beta-thalassemia major. Indian J Pediatr. 2005;72:159-64.

IN A NUTSHELL

1. Endocrine disorders occur more often in poorly chelated thalassemics due to iron deposit in the endocrine glands, hence effective chelation therapy is important.
2. Short stature, hypogonadism and osteoporosis may occur even in the well-chelated thalassemic children.
3. Good nutrition improves the hypermetabolic state of thalassemics, improves the growth and reduces the risk of osteoporosis.
4. Symptoms of endocrine disease may be subtle, hence regular screening for complications is important.
5. Post-BMT, thalassemic children should be screened for late endocrine complications due to pre BMT iron overload.

Chapter 44.32
Endocrine Effects of Radiation and Cancer Chemotherapy

Margaret Zacharin

Over the past 30 years, the cure rate for children and adolescents with cancer has markedly improved so that approximately 80% of children and young adolescents currently diagnosed with malignancy can be expected to be cured, with even higher survival rates for those who have had acute lymphoblastic leukemia or Hodgkin disease. However, only around 70% of survivors are aware of an accurate diagnosis of their past disorder and only around 30% are aware of the need for long-term follow-up for future health problems related to past treatment.

Health problems detected later in life are related both to the type of past treatment and to the lifestyle of the survivor. One in an estimated 650 adults is now a survivor of childhood cancer. For these reasons, long-term follow-up is essential. All those who look after young people, who have had childhood cancer need to be aware of the potential problems that cover almost all bodily systems including the endocrine system.

GENERAL PROBLEMS

New Malignancy Risk
Twenty five years after diagnosis, approximately 4% of survivors will develop a second tumor (6 times the population risk), 1 in 180 will develop a non-CNS second malignancy. A large study of survivors undertaken 20 years after diagnosis, found 18.1% had died, mainly due to subsequent neoplasms, cardiac or pulmonary causes, the major identified risks being a history of radiotherapy, alkylating agents or epipodophyllotoxins.

Cardiotoxicity
This is a major cause of late morbidity and is important for endocrine management. High body mass index (BMI), ischemic heart disease, hyperlipidemia and diabetes risks are all linked to a history of brain or bone tumors. Chest radiation and anthracycline related chemotherapy increase risks for ischemic heart disease.

Quality of Life
Quality of life in childhood cancer survivors, particularly those who have been exposed to brain radiation, is well recognized to be decreased in areas of physical health, difficulty in daily life, psychological stress including depression, eating disorders and social adaptation. Survivors are less likely to undertake tertiary education, have more unemployment and lesser chances of marriage.

Neurocognitive Problems
These occur in children as a result of radiation to the whole brain or focal radiation and also with high dose methotrexate or cytarabine and with intrathecal chemotherapy. Girls appear to be at higher risk than boys for neurotoxicity. Surgery adversely affects neurocognitive function in some children. The younger the child at the time of treatment, the more likely will be problems with short-term memory, learning difficulties and concentration. Neuropsychological testing can help to assess problems. Repeat testing should be done at key transition times (early primary school, into middle school, and before senior school).

Growth
Growth from childhood into adulthood can be altered if the hypothalamus and/or pituitary gland are affected. Radiation treatment to bones results in reduced bone growth that is not overcome by the effect of hormones. Final height is thus affected by both hormone deficiencies and bone growth.

ENDOCRINE PROBLEMS

The hypothalamus, pituitary, thyroid, adrenal and gonads are all at potential risk. Problems are more commonly seen in older patients, after stem cell transplant, and in those who had radiation. In a study of pediatric and young adult survivors of non-CNS malignancy, more than half had associated endocrine conditions, often with more than one condition in each patient. As with all chronic health conditions, an indoor lifestyle is common, with reduced sun exposure, low vitamin D and consequent implications for bone health.

Radiation Effects on the Hypothalamus and Pituitary
Cranial radiation as part of cancer treatment can either be administered as high dose focal radiation directed at a brain tumor, usually around 40–54 Gy; whole brain radiation of 12–18 Gy as used for treatment of some types of high risk leukemia or after neurological relapse of leukemia or lymphoma; or as part of total body radiation (12 Gy) as conditioning treatment prior to bone marrow transplant.

Hypothalamic pituitary damage It is likely after most focal radiation, which includes the base of skull, including radiation for posterior fossa tumors. The major damage is usually to the hypothalamic area, so that releasing hormones are more impaired than pituitary hormones themselves, making assessment potentially difficult. Stimulation tests for pituitary function can be misleading as it is the releasing hormones that are missing. Formal testing may appear normal.

Growth hormone (GH) is the most commonly adversely affected pituitary hormone after radiation exposure, most often occurring within 1–4 years of radiation.

Thyroid stimulating hormone (TSH) may be lost after cranial radiation. However, scatter radiation to the thyroid from cranial radiation (focal or whole brain) may also cause primary hypothyroidism. Mild to moderate hypothyroidism is often impossible to detect clinically in a child and may only be evidenced by reduced linear growth.

Adrenocorticotropic hormone (ACTH) deficiency is generally reported as occurring in about 15% of those exposed to cranial radiation. It is difficult to assess, with stimulation tests for adrenal reserve being inaccurate. Regular early morning cortisol levels, in conjunction with a history of increasing tiredness, need for rest during or after school, are all indicative of possible cortisol deficiency and might indicate the need for cortisol replacement on a daily basis. Sometimes only steroid cover for stress is needed. The major importance of recognizing ACTH deficiency is due to its subtlety. It can be extremely dangerous when unrecognized, such as in the context of acute intercurrent illness, fracture or general anesthesia. It is very easily treated, with consequently improved safety for the patient.

Gonadotropins The timing and tempo of puberty is altered after cranial radiation, with a triphasic pattern seen. The earlier the radiation exposure, the earlier the likelihood of onset of puberty due to disinhibition of normal hypothalamic restraint on puberty, in both boys and girls. However, the likelihood of gonadotropins remaining normal 10–12 years after cranial radiation is extremely low (see later section for further discussion).

Antidiuretic hormone Diabetes insipidus does not occur due to brain radiation. However, it is likely when a tumor is located in the midline hypothalamic pituitary area, either due to the position or due to size of the tumor or by any necessary surgery.

GROWTH MONITORING IN CANCER SURVIVORS

When seeing a child or adolescent treated with cancer in the past, it is necessary to take a clear history of the treatment regime and ages at which treatment was given, together with doses of radiation and chemotherapy, extent of surgery and any complications found at any time during the treatment period. Assessment must also include normal features of growth and development of the child within his or her family. Prenatal influences, perinatal health problems, birthweight, growth in the first 2 years of life and a history of timing of puberty of family members are essential, in order to create a construct as to an expected growth pattern for any individual. Careful plotting of a growth chart for both height and weight, in the context of the mid-parental height expectation is essential when making estimates of current and future height predictions and evaluation of possible growth failure or excess. In addition, a careful evaluation of upper versus lower segment growth is essential in follow-up, as spinal irradiation will diminish spine growth.

Childhood cancer treatments are likely to result in poor health, reduced appetite and weight loss over the first months of treatment. This is usually followed by a period of poor linear growth, due to reduced nutritional status. As nutrition improves and weight gain recommences, linear growth is likely to improve. It is then possible to observe a second fall off in growth velocity that might suggest growth hormone deficiency at a time of good nutrition.

Plotting of normal linear growth on a growth chart will prevent the need for unnecessary repeated growth hormone stimulation tests. These should only be undertaken if there is deterioration in growth rate, out of keeping with growth expectation. For example, if a child has entered puberty and a pubertal growth spurt is expected but not happening, one should suspect the advent of growth hormone deficiency.

Conversely, if puberty occurs at any age, one should expect to see acceleration in linear growth rate. This acceleration can only occur if growth factors are adequate, sex hormones are functioning and the skeleton is capable of responding to the stimuli. Given that growth hormone deficiency, early puberty, and poor axial skeletal growth due to earlier radiation, are all potential operative factors for children who have had cancer, all of these factors need to be taken into consideration. All can be read from a growth chart, if carefully and consistently plotted.

ENDOCRINE DISORDERS AFTER CHILDHOOD CANCER

Pituitary

Growth hormone (GH) deficiency is marked by a significant reduction in growth velocity, crossing height centiles. However, a combination of slowing growth from GH deficiency, rapid growth of early puberty and poor spinal growth can cause great confusion with interpretation. Childhood spinal radiation results in inevitable loss of around 10 cm of final height, due to direct radiation damage to vertebral bone. If radiation is delayed to around the age of 10 years, only about 5 cm of final height is irrevocably lost.

Other pituitary hormone losses can occur at variable intervals after brain radiation exposure. Gonadotropins, ACTH and thyroid-stimulating hormone (TSH) are generally considered to be lost in that order, though it is quite variable and not all patients will have losses of more than one hormone. However, 8–10 years after radiation exposure, the chance of multiple pituitary hormone deficits is extremely high.

Thyroid

A mixture of primary and secondary hypothyroidism can occur after cranial radiation or craniospinal radiation, with scatter radiation being a significant component. Careful attention to circulating thyroid hormones as well as TSH is necessary for accurate diagnosis.

Nodularity and malignancy risk after radiation exposure rise with time, to 20 times population risk 20 years after diagnosis. Routine ultrasound surveillance every 2 years is necessary.

Gonads

Hormone replacement treatment is required for all those, either male or female, who are hypogonadal, to improve any remaining linear growth, feminization or virilization, normalization and maintenance of good skin tone and texture, good muscle bulk, general health and accrual of normal adult bone quality.

Testis

Chemotherapy Damage to the gonads is most commonly seen with alkylating agents including cyclophosphamide, busulfan, melphalan, and chlorambucil. Chemotherapy administered after puberty causes permanent loss of fertility, but maintenance of Leydig cell function. The prepubertal testis is not protected. Patients treated without cyclophosphamide often recover complete endocrine function with normal sperm, number and quality, whereas high-risk protocols including cyclophosphamide result in severe reduction in number of sperms.

Radiation to the testis of only 4 Gy causes complete permanent azoospermia. Doses between 12–20 Gy also damage Leydig cells.

As a result of these complex and evolving problems consideration is now being given to offer attempted sperm salvage prior to treatment for all boys of any age who are about to undertake any form of cancer treatment involving chemotherapy and radiation.

Ovary

Chemotherapy As girls have all their ova for life at birth, all chemotherapy at any age causes follicular loss. The older the girl at the time of treatment the less likely will be ovarian recovery. Young women who have had childhood cancer treatment should be advised to consider pregnancy under the age of 30, if appropriate and desired, to reduce disappointment due to likelihood of early menopause.

Radiation causing ovarian damage occurs at the time of conditioning treatment prior to bone marrow transplant or with local pelvic radiation.

Problems Associated with Gonadal Management after Childhood Cancer Treatment
- There are unresolved potential ethical issues concerning parents choosing to remove reproductive tissue from a child or adolescent below the age of informed consent for the purposes of possible reproduction in future, particularly if there is a risk to the patient in taking the tissue.
- Fertility is frequently achievable only with donor gonadal tissue.
- Cerebral arteritis is a complication of brain radiation, with a major increase in relative risk for stroke. Consideration may need to be given to choose use of transdermal estrogen, to reduce coagulopathy of oral estrogen.
- Direct uterine radiation increases the risk of a small uterus with reduced elasticity and vascular supply and results in increased fetal loss and increased risk for small gestational age infants.
- Complexities of pregnancy management also include cardiovascular and respiratory problems.

IN A NUTSHELL

1. One in an estimated 650 adults is now a survivor of childhood cancer. Health problems detected later in life are related both to the type of past treatment, including chemotherapy and radiation, and to the lifestyle of the survivor.
2. Some of the problems envisaged include new malignancy risk, cardiotoxicity, endocrinopathies, and issues related to neurocognition and poor quality of life.
3. Endocrinopathies relate to the organ of irradiation and certain chemotherapies and include hypothalamus and pituitary damage, hypothyroidism and thyroid malignancy, gonad damage and bone health.
4. Radiation and chemotherapy effects on non-endocrine organs such as the heart, breast, kidney, teeth, lungs, GIT, eyes, bladder and liver are important to be kept in mind for long-term surveillance.
5. Preventive therapy for all these anticipated issues will greatly improve long-term health of children with cancer.

MORE ON THIS TOPIC

Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27:2328-38.

Darzy KH, Shalet SM. Hypopituitarism following radiotherapy revisited. Endocr Dev. 2009;15:1-24.

Ishida Y, Sakamoto N, Kamibeppu K, et al. Late effects and quality of life of childhood cancer survivors: Part 2. Impact of radiotherapy. Int J Haematol. 2010;92:95-104.

Littley MD, Shalet SM, Beardwell CG, et al. Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf). 1989;31:363-73.

Maule M, Scélo G, Pastore G, et al Risk of second malignant neoplasms after childhood central nervous system malignant tumours: an international study. Eur J Cancer. 2008;44(6):830-9.

Merchant TE, Rose SR, Bosley C, et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. J Clin Oncol. 2011;29:4776-80.

Ness KK, Hudson MM, Ginsberg JP, et al. Physical performance limitations in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009;27: 2382-9.

Patterson BC, Wasilewski-Masker K, Ryerson AB, et al. Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program. J Clin Endocrinol Metab. 2012;97:810-8.

Chapter 44.33
Adult Consequences of IUGR and Prematurity
Sarah Mathai, Paul Hofman

Adult diseases like type 2 diabetes mellitus (T2DM), coronary artery disease (CAD) and hypertension result in chronic morbidity because of their therapeutic limitations and thereby pose a major public health burden. With improvement in life expectancy, there is a predicted global increase of people greater than 65 years of age. Therefore, public health experts are now focusing on prevention of these diseases rather than their cure. In the search for preventable causes for noncommunicable diseases, Professor Barker and his colleagues observed an increased risk of diabetes and coronary artery disease (CAD) in men who were born with low birthweight (LBW). Currently, there is convincing evidence that an adverse periconceptual/fetal/neonatal environment may predispose individuals to developing later adult diseases.

The diabetes epidemic is particularly relevant for South Asian countries especially India. Among the predicted 366 million people with diabetes by the year 2030, almost 80 million are expected to be in India. Up to 30% of Indian children are born LBW either at term or preterm. If indeed LBW does predispose to later diseases, India will have the maximum impact. Hence, pediatricians need to be aware of the potential consequences of intrauterine adversity on the long-term health of the population.

ADVERSE EARLY LIFE EVENTS AND LATER ADULT DISEASES

Professor Barker and his colleagues postulated a link between LBW and later adult diseases (Barker hypothesis) which states *adverse intrauterine events impairing fetal growth permanently alter the structure and physiology of the offspring, such that the risk of adult onset diseases is increased*. Since then, several studies worldwide have confirmed this association. In addition to the metabolic syndrome (obesity, T2DM, hypertension, stroke and CAD), LBW has been associated with chronic obstructive airways disease, osteoporosis, psychiatric disorders, glucose intolerance, hyperinsulinism, dyslipidemia, and hyperuricemia.

Birthweight, however, is a relatively poor marker of intrauterine adversity. Impaired growth due to early gestational adversity may recover and result in normal birthweight but may still have metabolic perturbations. Thus, offspring of pregnant women exposed to the Dutch famine in early/mid gestation, despite having normal birthweight, had increased risk of obesity, breast cancer, obstructive airways disease, etc.

Like LBW, other groups at risk of intrauterine adversity include those born preterm/post-term, twins, offspring of gestational diabetic mothers and in vitro fertilization (IVF) offspring. Metabolic abnormalities and blood pressure changes have been reported in twins, preterms and recently in those born post-term. Sexual dimorphism has also been reported with accentuation of the adverse phenotype in men.

Although scarce, there is some human data showing evidence for intergenerational transmission of the changes associated with intrauterine adversity. Grandchildren of women exposed in utero to the Dutch famine had reduced birthweight. Intergenerational transmission of obesity was shown recently in a large Finnish cohort. Another recent study also demonstrated increased abdominal adiposity in term-born children of preterm parents indicating that adverse outcomes associated with preterm birth may extend to the next generation.

INDIAN SCENARIO

Most of the studies worldwide reported lower birthweight per se as an independent determinant of increased risk for later diseases, although the risk increases with rapid postnatal weight gain. However, the Indian scenario is slightly different. The Pune study described Indian newborns as having a *thin-fat* phenotype being shorter, lighter with less muscle mass but with increased subcutaneous fat. In Mysuru, an increased prevalence of T2DM was noted in those born short but with a high ponderal index. In the Delhi and Vellore cohorts, thinness at birth along with accelerated weight gain either after the age of 2 years (Delhi) or during adolescence (Vellore) predicted an increased risk of T2DM. Rapid weight gain predicted the risk although they were not obese during childhood. These studies suggest that along with LBW, postnatal factors, particularly increased food availability and adiposity, also play an important role in increasing the diabetes risk in India. This was elegantly showed in the rural Vellore LBW men. These young men, who continued to live in their rural environment, had low body mass index (BMI)/waist circumference and showed only subtle risk factors for T2DM.

FETAL PROGRAMMING

Different organ systems develop during specific periods of fetal life known as *critical periods*. Environmental insult such as maternal undernutrition, placental insufficiency, chronic maternal illness (e.g., renal disease) or other physical stress occurring during critical periods is postulated to result in *fetal programming*. Programming is defined as the permanent changes/adaptations occurring during critical periods of development resulting in long-term changes in structure and function. These adaptations can become maladaptive in later life and form the basis for the developmental origins of adult diseases. As human development continues postnatally, this critical period of developmental plasticity extends from the periconceptual period to infancy.

Fetal adaptations may result in phenotypic changes such as babies who are proportionately small with early gestational nutritional insufficiency or LBW disproportionate babies with later gestational insult. Adaptations may also induce permanent changes like reduced number of nephrons, cardiomyocytes, pancreatic β-cells and skeletal myocytes which may result in reduced function of these organs and thereby predispose to later diseases.

Several mechanisms have been proposed to explain fetal programming. The *thrifty genotype* postulates that thrifty genes with enhanced capacity to store fat, selected during fetal undernutrition, increases the risk of obesity and T2DM when exposed to increased food in later life. The *thrifty phenotype* states that fetal adaptations which during intrauterine adversity promote growth of vital organs at the expense of less essential organs, may become maladaptive in later life. The *fetal salvage* hypothesis supports this and further proposes that fetal redistribution of glucose to vital organs occurs primarily by developing peripheral and/or hepatic insulin resistance. The *predictive adaptive response* (PAR) hypothesis proposes that fetal adaptations occur predicting a later environment based on the fetal environment. If there is a mismatch in the later environment, the PAR may become maladaptive.

Mechanisms involved in programming include epigenetics, oxidative stress and mitochondrial dysfunction. *Epigenetics* is a phenomenon that regulates gene expression without altering the DNA structure. Thus, environmentally induced changes can result in permanent phenotypic changes. The most extensively studied epigenetic mechanisms are DNA methylation and histone modification and both are affected by nutrition. Inadequate diet may result in altered DNA methylation states as methylation reactions are highly dependent on dietary glycine, folate and vitamin B_{12}. Recently in the Pune cohort, low maternal vitamin B_{12} was shown to predict insulin resistance and adiposity in their children. Another mechanism is oxidative stress-induced programming resulting from dietary deficiency of antioxidants. This forms the basis for trial of antioxidants supplementation in high-risk pregnancies and preterm infants.

Link between Fetal Programming and Later Diseases

Two consistent abnormalities demonstrated in all age groups of those born LBW and preterm are a reduction in insulin sensitivity and a tendency for obesity, particularly abdominal obesity.

Insulin Sensitivity, Insulin Resistance and Compensatory Hyperinsulinemia

Insulin regulates the uptake, assimilation and storage of glucose, amino acids and fatty acids. While it is primarily a hepatic hormone, being released into the portal circulation, it has important peripheral action. Its role in glucose metabolism includes inhibition of hepatic gluconeogenesis and glycolysis, promoting glycogen storage and increasing glucose uptake by insulin-sensitive tissues (such as muscle and fat). Almost 75% of the insulin-dependent glucose uptake occurs in skeletal muscle. In the adipose tissue, insulin inhibits hormone-sensitive lipoprotein lipase which converts triacylglycerol into glycerol and fatty acids. The ability of insulin to stimulate glucose uptake in tissues and suppress hepatic glucose release is known as *insulin sensitivity*.

Insulin resistance refers to a pathological decrease in insulin sensitivity. It can either be peripheral (skeletal muscle, adipose tissue) or hepatic and these two can coexist. If there is a reduction in insulin sensitivity, a compensatory increase in insulin secretion occurs to maintain euglycemia. Thus, apparently healthy individuals with reduced insulin sensitivity have higher plasma insulin levels.

Selective Insulin Resistance and Its Role in the Pathogenesis of Various Diseases

In addition to metabolic effects, insulin is also involved in cell proliferation, sodium retention, sympathetic stimulation, vascular hypertrophy and endothelial function. Insulin action is mediated by two major insulin signaling pathways: the phosphatidylinositol (PI) 3-kinase pathway which mediates the metabolic (glucose transport, glycogen and lipid synthesis) and mitogenic actions of insulin and insulin-like growth factor 1 (IGF-1). The second one is the *Erk* mitogen-activated protein (*Erk* MAP) kinase pathway which contributes solely to the nuclear function, cellular differentiation and mitogenic effects of insulin. As insulin resistance involves only the *metabolic effects of insulin*, insulin signaling along PI 3-kinase pathway is impaired, while hyperinsulinemia may result in overactivation of the MAP kinase pathway with its detrimental effects.

Thus, chronic hyperinsulinemia may have excess effect on other organs contributing to dyslipidemia, hypertension and endothelial dysfunction. Long-term insulin resistance has been shown to markedly increase the risk of T2DM, hypertension, CAD, stroke, metabolic syndrome and cancer.

Adipocyte Programming

Those born LBW and preterm are at risk for increased adiposity. It is postulated that adipocytes programmed during critical periods may have altered function and later predispose to increased adiposity. The most important environmental factor that adversely affects insulin resistance is adiposity. The pathogenesis in insulin resistance is therefore amplified by rapid postnatal weight gain. Distribution of fat is also important with truncal adiposity consistently being linked with insulin resistance.

IN A NUTSHELL

1. Adverse early life events such as small for gestational age (SGA) and prematurity may predispose individuals to later adult diseases like T2DM.
2. These maladaptations may be inheritable and persist across generations.
3. India will have the maximum impact as India tops the world in LBW births and the number of people with diabetes.
4. Along with measures to reduce LBW, preventive lifestyle modifications such as healthy diet and regular physical exercise reduces the risk of later adult diseases.

MORE ON THIS TOPIC

Barker DJ, Winter PD, Osmond C, et al. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2:577-80.

Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med. 2004;350:865-75.

Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. J Clin Endocrinol Metab. 2001;86:3574-8.

Fall CH, Stein CE, Kumaran K, et al. Size at birth, maternal weight, and type 2 diabetes in South India. Diabetes Med. 1998;15:220-7.

Lapillonne A, Griffin IJ. Feeding preterm infants today for later metabolic and cardiovascular outcomes. J Pediatr. 2013;162:S7-16.

Longo S, Bollani L, Decembrino L, et al. Short-term and long-term sequelae in intrauterine growth retardation (IUGR). J Matern Fetal Neonatal Med. 2013;26:222-5.

Mathai S, Derraik JG, Cutfield WS, et al. Increased adiposity in adults born preterm and their children. PLoS One. 2013;8:e81840.

Raghupathy P, Antonisamy B, Geethanjali FS, et al. Glucose tolerance, insulin resistance and insulin secretion in young south Indian adults: relationships to parental size, neonatal size and childhood body mass index. Diabetes Res Clin Pract. 2010;87:283-92.

Thomas N, Grunnet LG, Poulsen P, et al. Born with low birth weight in rural Southern India: what are the metabolic consequences 20 years later? Eur J Endocrinol. 2012;166:647-55.

Yajnik CS, Fall CH, Coyaji KJ, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. Int J Obes Relat Metab Disord. 2003;27:173-80.

Section Editors Brijesh Arora, Shripad Banavali

Chapter 45.1

Epidemiology of Cancers in Children

Ramandeep Singh

Cancer is the leading cause of death worldwide accounting for 8.2 million deaths in 2012. It is generally regarded as a disease of adults with less than 1% of cancer in the developed countries occurring in children less than 15 years of age. However, in India where the children comprise more than a third of the population, the proportion of childhood cancers can be up to 5% of all cancer burden. It is estimated that worldwide there are 200,000–250,000 new cases of cancer occurring in children less than 15 years of age every year, out of which 40,000–50,000 occur in India.

INCIDENCE OF CHILDHOOD CANCER

The incidence of childhood cancer in most populations in the world ranges from 7/100,000 to 16/100,000 person years (PYs). In childhood populations of Europe, North America and other developed regions of the world, cancer incidence rates are around 14/100,000 PYs. Cancer incidence in the developing countries is less well known, because there have been fewer population-based cancer registries (PBCRs) with adequate completeness.

Based on analysis of the 2006 Indian National Cancer Registry Programme report (which covered 4.3% of the Indian population and 0.5% of the geographical area), the age-standardized incidence rate for childhood cancer in India ranged from 3.8/100,000 to 12.4/100,000 PYs. The reported incidence from urban PBCRs (Bengaluru, Bhopal, Chennai, Delhi, Mumbai) was generally higher than reported incidence from rural PBCRs (Barshi and Ahmedabad district) **(Fig. 1)**. There is some evidence to suggest that this rural-urban differential is predominantly from underdiagnosis although underascertainment and a truly lesser incidence of childhood cancer in rural India cannot be ruled out.

VARIATION IN INCIDENCE BY GENDER

Boys are around 20% more likely to develop cancer than girls but this male to female sex ratio in childhood cancer registration is not uniform in the world. An increased male to female cancer registration rate sex ratio (i.e., relatively more boys and lesser girls with cancer) has been inversely associated with a country's health, educational, social and economic indicators. This suggests a gender bias in diagnosing and registering cases in some developing countries.

The reported incidence of childhood cancer in India in males (3.9–15.0/100,000 PYs) is higher than in females (2.3–9.7/100,000 PYs) in almost all PBCRs **(Fig. 1)**. As incidence rates automatically adjust for the sex ratio in the underlying population, there have to

be other reasons for this relatively higher incidence of childhood cancer in males seen in India. Gender bias in seeking health-care, including treatment of cancer, is one possible explanation although other biological and etiological possibilities cannot be ruled out.

VARIATION IN INCIDENCE BY TYPE OF CANCER

Unlike adult cancers which are mainly carcinomas, childhood cancers have a diverse histology and are hence grouped into twelve main cancer groups [International Classification of Childhood Cancer (ICCC)] based on morphology **(Fig. 2)**. Overall, the three most common cancers in childhood comprise of leukemia, brain tumors and lymphoma, although this varies across different populations. In developed countries, around one-third of childhood cancers are leukemias, one-fourth are brain tumors followed by the remaining childhood cancers **(Fig. 2)**. In contrast, in tropical Africa, Burkitt lymphoma [a type of non-Hodgkin lymphoma (NHL)] is often the most common childhood cancer.

In India **(Fig. 2)**, leukemia is the most common childhood cancer with relative proportion varying between 25% and 40%. About 60–80 percent of all leukemias reported are acute lymphoblastic leukemia (ALL). In contrast to the developed world, in India lymphomas often exceed central nervous system (CNS) tumors, particularly in males. Not only is the proportion of lymphomas higher in India, but Hodgkin lymphoma exceeds NHL, a pattern opposite to that seen in the developed world. The rarer registration of CNS tumors in India is at least partly due to underdiagnosis. A relative paucity of neurodiagnostic and neurosurgical facilities, which leads to missed diagnosis in those presenting with headache, seizures, and altered sensorium, could explain the differences in incidence in India.

There is a reported excess of retinoblastoma in India (also seen in Pakistan and sub-Saharan Africa). It is likely that some of this excess is, because of better diagnosis and recognition of retino-blastoma, which, once at an advanced stage, is easy to identify.

VARIATION IN INCIDENCE WITH TIME

The incidence of childhood cancer is increasing by around 1% every year in Europe, but the rate of change as well as the direction is different for individual cancer types. These increases are larger for CNS tumors and lesser for lymphomas and leukemias. On the other hand, the incidence of bone tumors, liver tumors, and retinoblastoma is unchanged. Part of these increases can be explained by changes in diagnostic methods and registration practices, but other environmental and lifestyle factors may have a role. Continued development of noninvasive diagnostic methods such as computerized tomography, magnetic resonance imaging and nuclear medicine scans has increased the accessibility, the timeliness and the precision of diagnosis. These advances probably explain, at least in part, the rapid increase in the incidence of CNS tumors observed in recent decades, as well as their relatively lower incidence rates in developing countries.
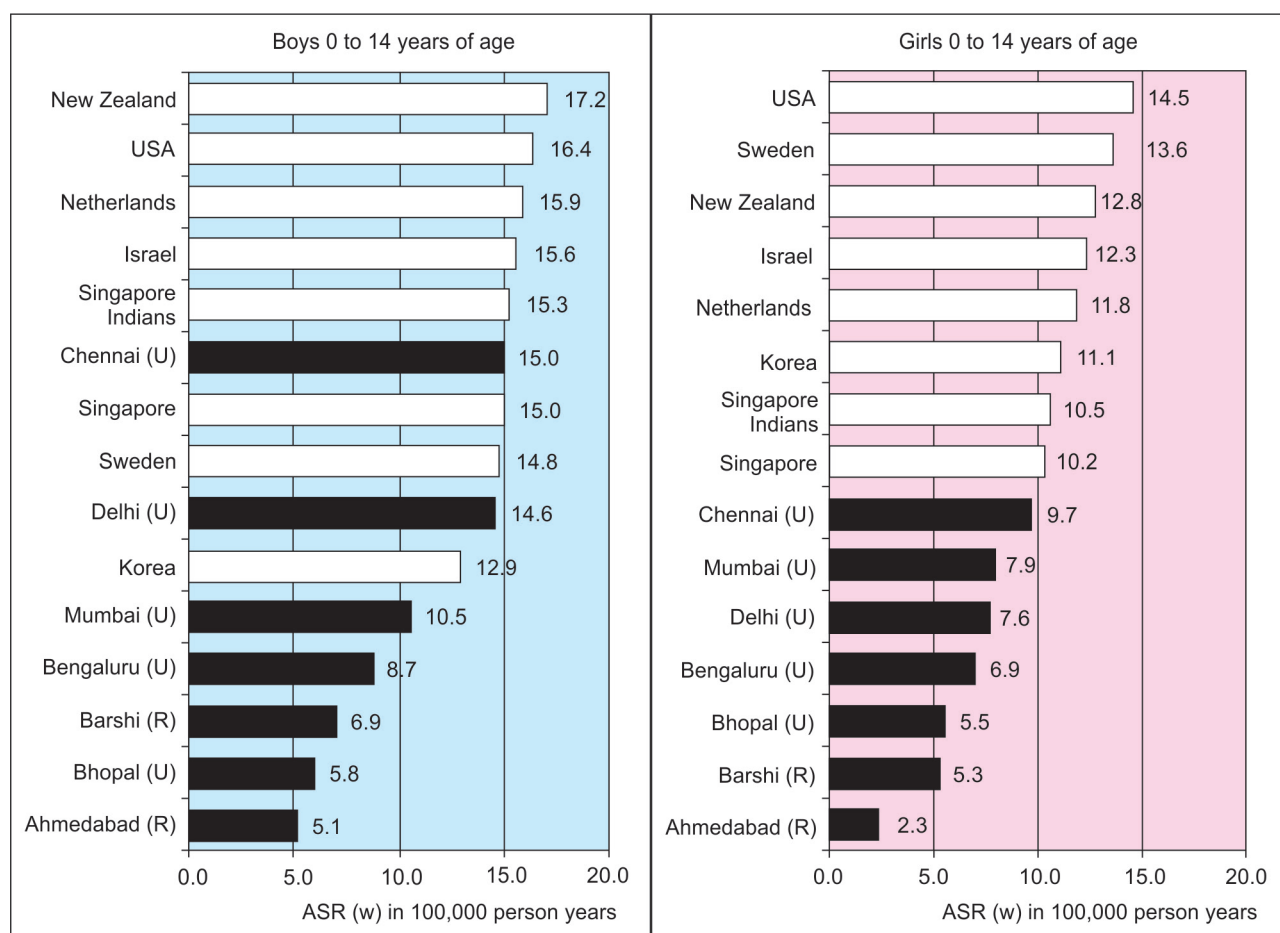
Figure 1 Sex-specific age-standardized childhood cancer incidence rates [ASR(w)] for rural (R) and urban (U) Indian population-based cancer registries (PBCRs) and selected PBCRs from the world
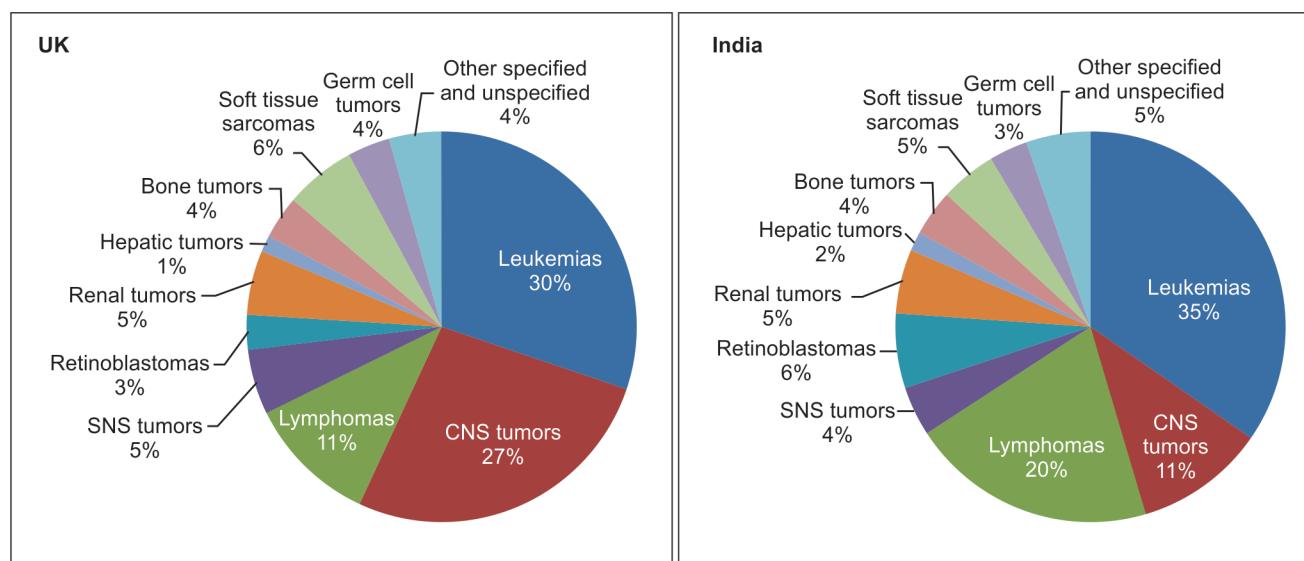
Figure 2 Distribution of childhood cancer based on International Classification of Childhood Cancer in the United Kingdom and India (Chennai)
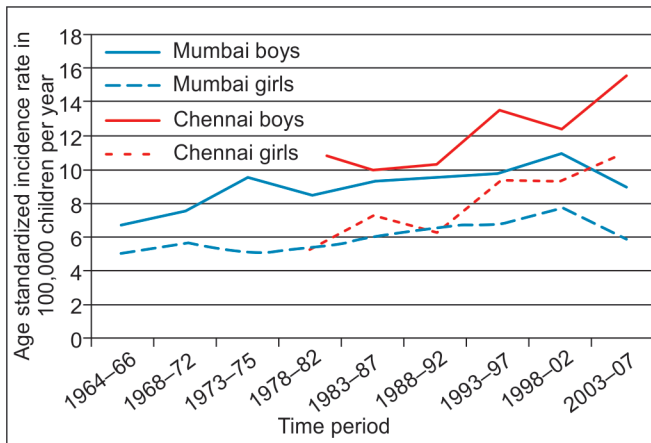
Figure 3 Longitudinal time trends in incidence of childhood cancer in boys and girls less than 15 years of age in Mumbai and Chennai population-based cancer registries (PBCRs)

In India, longitudinal data of sufficient duration is available only for a very few number of PBCRs. As **Figure 3** shows, the reported incidence of childhood cancer has increased over the last 50 years in Mumbai and last 30 years in Chennai. Any changes in incidence pattern can occur from a true change and also from changes in disease recognition, diagnosis and registration.

ETIOLOGY OF CHILDHOOD CANCER

The causes of majority of childhood cancers are unknown and a few established causal associations (genetic/congenital or environmental) only explain a small proportion of cases. **Table 1** summarizes our current knowledge of the known risk factors associated with causing childhood cancers. Overall, the heritable component of childhood cancer is estimated to be around 2–3% at most. Notable among these are germline mutations in the *rb* gene and the *p53* gene associated with hereditary retinoblastoma syndrome and Li-Fraumeni syndrome respectively. For certain rare cancers like retinoblastoma, optic glioma, adrenocortical carcinoma and pheochromocytoma, the heritable component can be up to 40% or higher. Besides the known hereditary syndromes, there is no excess risk of cancer in siblings, parents or offspring of children with cancer.

Because of its onset early in life, exposure to environmental factors either in utero or after birth may be less important than for cancers developing in adults. Only a few exposures, mostly exceptional, have been shown to cause cancer in children. For example, an increased incidence in thyroid cancer has been seen in children living in the countries surrounding Chernobyl after the radioactive fallout from the accident there. Use of diethylstilbestrol in the 1970s in pregnant women for morning sickness was associated with increased risk of vaginal cancer in the female offspring. Besides this, a number of other environmental risk factors have been studied including nonionizing radiation, maternal smoking, alcohol consumption and diet, paternal occupation, exposure to various chemicals such as benzene, nitrosamines, pesticides, hair dyes and some medications, etc. Till date, their role in the causation of various childhood cancers has not been established.

MORTALITY AND SURVIVAL

Cancer is an important contributor to death in children but its relative contribution varies. In the United Kingdom, cancer is the

Table 1 A selection of known risk factors and associations for childhood cancer

Risk factors and associations	Childhood cancers
Familial neoplastic syndromes	
Familial retinoblastoma	Retinoblastoma, osteosarcoma
Li-Fraumeni syndrome	Soft tissue sarcoma, osteosarcoma, CNS tumors, adrenocortical carcinoma
Neurofibromatosis type 1	Astrocytoma (optic glioma), ALL, JMML, rhabdomyosarcoma
Hereditary nonpolyposis colon cancer	Glioma
Familial adenomatous polyposis	Medulloblastoma, hepatoblastoma
Gorlin syndrome	Medulloblastoma (desmoplastic variety), basal cell carcinoma
Inherited immunodeficiency syndromes	
Ataxia-telangiectasia	Lymphoma, leukemia
Wiskott-Aldrich syndrome	NHL
Bloom syndrome	NHL, Wilms tumor, osteosarcoma
Common variable immunodeficiency	Lymphoma
IgA deficiency	Lymphoma
Severe combined immunodeficiency	Lymphoma
Bone marrow failure syndromes	
Fanconi anemia	AML, myelodysplasia
Diamond-Blackfan anemia	AML, osteosarcoma
Shwachman-Diamond syndrome	Myelodysplasia
Miscellaneous genetic syndromes and chromosomal disorders	
Down syndrome (trisomy 21)	AML, ALL, germ cell tumors
Klinefelter syndrome (XXY)	Germ cell tumors
WAGR syndrome	Wilms tumor
Denys-Drash syndrome	Wilms tumor
Beckwith-Wiedemann syndrome	Wilms tumor, hepatoblastoma, neuroblastoma, pancreatoblastoma
Rothmund-Thomson syndrome	Osteosarcoma
Tuberous sclerosis	Subependymal giant cell astrocytoma
Environmental/exogenous carcinogens	
Ionizing radiation (antenatal diagnostic X-rays, therapeutic radiotherapy)	ALL, CNS tumors, osteosarcoma
Alkylating chemotherapy drugs	AML, osteosarcoma
Epstein-Barr virus	Hodgkin disease, Burkitt lymphoma, nasopharyngeal carcinoma
Human immunodeficiency virus	NHL, Kaposi sarcoma
Hepatitis B virus	Hepatocellular carcinoma

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; JMML, juvenile myelomonocytic leukemia; NHL, non-Hodgkin lymphoma.
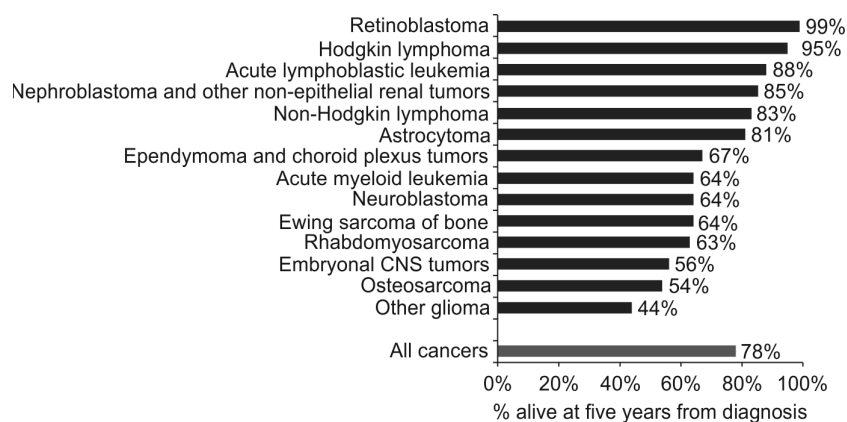
Figure 4 Five-year survival rates for selected childhood cancers, Great Britain, diagnosed during 2001–2005 (Obtained from http://www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer/survival/#Five-year. Accessed December 3, 2014)

most common cause of disease-related death (20%) in children and after injuries (21%) the most common cause of death in children overall. Despite cancer being the most common cause of disease-related death in children in the developed world; with improving survival rates, the mortality rate has declined to approximately 3/100,000 children/year. In contrast to the developed world, cancer accounts for less than 1% of childhood deaths in developing countries, where deaths from infectious diseases are much more prominent.

Tremendous progress has been made in the management of children with cancer. Since the 1960s, when most children who were diagnosed with cancer died, in the 21st century, nearly 80% of children are cured when timely and optimal treatment is available, accessible and completed **(Fig. 4)**. This improvement of survival reported from developed countries has resulted from increasing use of intensive chemotherapy combined with other modalities of treatment, improved generalized supportive management, application of results of clinical trials and centralization of care permitting each patient to benefit from the best of the multidisciplinary expertise and technology available for these rare conditions. The prognosis differs by tumor type, with highest survival for retinoblastoma, thyroid carcinoma, Hodgkin lymphoma, etc. Lowest survival is observed for some CNS tumors, certain leukemias and some sarcomas of bone and soft tissues.

However, this progress has not been equitable across the world **(Fig. 5)**, with less than 20% of the children with cancer diagnosed annually worldwide achieving these outcomes. In developing countries where more than 80% of childhood cancer cases and nearly 95% of childhood cancer deaths occur, the management of cancer in children still poses enormous challenges. Even for childhood cancers which would have a 5-year survival of greater than 90% in developed countries, like ALL and Wilms tumor, the combination of high treatment abandonment, toxicity-related mortality and disease progression in developing countries results in poor outcomes.

The less favorable outcome in the developing countries can be attributed to late diagnosis, unavailability of treatment, therapy abandonment, prior undernourishment, inadequate supportive therapy and unsuccessful follow-up. All these factors relate to lack of financial resources to support efficient health-care system for childhood cancer patients. In India, comparable outcomes to developed countries have been demonstrated in single-institution series. However, one cannot extrapolate these results to the whole population as often those who abandon treatment or are lost to follow-up are excluded from the analysis of hospital case series,
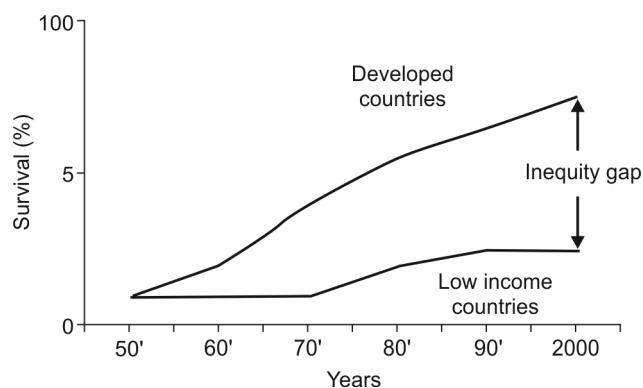
Figure 5 The survival gap of children with cancer (Masera G. Geographic hematology: an evolving concept. Haematologica. 2000;85:785-6. Obtained from: http://www.haematologica.org. Accessed December 3, 2014)

and such patients may have a more advanced disease and a poorer outlook. PBCR survival data is a better representation of cancer outcomes across India and survival rates have only been reported from urban PBCRs in Bangalore (1980s) and Chennai (1990s) where the 5-year overall survival for all childhood cancers combined was 37–40%. The highest survival in India was seen for Wilms tumor and Hodgkin disease where approximately two-thirds of the children survived for 5 years or more. The survival for retinoblastoma and germ cell tumors, which are cancers with excellent prognosis in the developed world, was however, disappointingly low and may be related to an advanced stage at presentation and suboptimal chemotherapy regimens used. Also low was the prognosis for leukemia and CNS tumors where approximately only 33% and 25% of the children survive at 5 years. There is no survival data from rural PBCRs, but it is likely to be still lower.

CANCER IN ADOLESCENTS

Cancer occurs rarely in adolescence (comprising ages 15–19 years) although the incidence is roughly twice as high as in children. Cancers in this age group include some childhood cancers (ALL, Hodgkin disease and CNS tumors), some *true* adolescent cancers like bone tumors (osteosarcoma and Ewing sarcoma) and germ cell tumors related to the growth and sexual changes in this age group, and appearance of some adult cancers like carcinomas and melanoma related to environmental exposure and lifestyle factors.

Adolescent cancers are often detected late. The overall population-based 5-year survival of adolescents with cancer is around 75% in developed countries. Improvement in survival of adolescent cancers has been slower relative to the progress in childhood cancers. The reasons for this may include delay in diagnosis, lower participation in clinical trials, poor compliance with treatment and psychosocial issues. There is no survival data from PBCRs on adolescents with cancer from India.

MORE ON THIS TOPIC

Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer. 2009;46:264-73.

Arora RS, Alston RD, Eden TO, et al. Cancer at ages 15–29 years: the contrasting incidence in India and England. Pediatr Blood Cancer. 2012;58:55-60.

Cancer in children. In: Boyle P, Levin B. World Cancer Report 2008. Lyon: International Agency for Research on Cancer; 2008. pp. 482-7.

Consolidated Report of Population Based Cancer Registries 2001-2004, National Cancer Registry Programme, Indian Council of Medical Research, Bangalore, India, 2006. From: www.icmr.nic.in/ncrp/report_pop_2001-04/cancer_p_based.htm. Accessed December 3, 2014.

Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. Cancer. 2008;112:461-72.

Nandakumar A, Anantha N, Appaji L, et al. Descriptive epidemiology of childhood cancers in Bangalore, India. Cancer Causes Control. 1996;7:405-10.

Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010;28:2625-34.

Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. Br Med Bull. 1996;52:682-703.

Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. Int J Cancer. 2008;122:2607-11.

Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64:83-103.

IN A NUTSHELL

1. Cancer in children is an uncommon disease and the incidence ranges from 7/100,000 to 16/100,000 PYs.
2. Boys are around 20% more likely to develop cancer than girls but this ratio is higher in some developing countries like India at least partly due to gender bias.
3. Overall, the three most common cancers in childhood comprise leukemias, brain tumors and lymphomas.
4. The incidence of childhood cancer is increasing, which can partly be explained by changes in diagnostic methods and registration practices, but other environmental and lifestyle factors may have a role.
5. The causes of majority of childhood cancers are unknown.
6. Currently nearly 80% of children are cured when timely and optimal treatment is available, accessible and completed. Outcomes in India are variable and at a population level reported 5-year overall survival for all childhood cancers combined is around 40% based on data published in 1990s.

Chapter 45.2
Acute Lymphoblastic Leukemia
Revathi Raj, Deenadayalan M

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates in a single B or T lymphocyte progenitor. ALL is the most common childhood malignancy and great strides have been made in the treatment of these children over the past four decades due to advances in combination chemotherapy, diagnostics, risk-adapted therapy and optimal use of hematopoietic stem cell transplantation (SCT).

INCIDENCE

Acute lymphoblastic leukemia is the most common malignancy diagnosed in patients younger than 15 years, accounting for 25–30% of all childhood cancers. The peak incidence is between 2 years and 5 years of age and it has a slight male preponderance. If one of the twins develops leukemia in the first 5 years of life, the risk of the second twin developing leukemia is about 20%. In India, out of 800,000 cancers diagnosed annually, about 50,000 are childhood cancer. Of these, 20–30% are diagnosed to have acute leukemia with approximately 8,000–10,000 children developing ALL every year.

Children with some genetic and immunodeficiency conditions like Down syndrome, Fanconi anemia, Bloom syndrome, Shwach-man-Diamond syndrome, ataxia-telangiectasia, neurofibromato-sis, Diamond-Blackfan syndrome, Poland syndrome, congenital agammaglobulinemia and Kostmann disease are more prone to get diagnosed with ALL as compared to the general population.

PATHOGENESIS

Initiation and progression of ALL is driven by complementary mutations that alter cellular functions. This could be an enhanced ability of self-renewal, a subversion of control of normal proliferation, a block in differentiation at early stages of white cell development or an increased resistance to apoptosis. Environmental agents such as ionizing radiation and chemical mutation have been implicated. However, in most cases, no etiologic factors are identified **(Fig. 1)**.

CLINICAL FEATURES (TABLE 1)

The presenting signs and symptoms of ALL reflect the degree of marrow failure and the extent of extramedullary spread. Pallor, fatigue, petechiae, purpura, bone pain and fever are the most common presenting features. Approximately 60% present with fever due to release of pyrogenic cytokines from the leukemic cells and fever resolves within 72 hours after the start of antileukemic

Figure 1 Molecular pathogenesis of acute leukemia

therapy. Lymphadenopathy, hepatomegaly and splenomegaly are manifestations of extramedullary leukemic infiltration. Anterior mediastinal mass can compress the great vessels and trachea and result in superior vena cava syndrome or the superior mediastinal syndrome. Patients with this syndrome present with cough, dyspnea, orthopnea, dysphagia, stridor, facial edema and increased intracranial pressure. This is more common in T-cell phenotype.

Patient with central nervous system (CNS) involvement may present with signs of increased intracranial pressure, cranial nerve palsies, hypothalamic syndrome, diabetes insipidus, chloromas of spinal cord and rarely hemorrhage especially in those presenting with high initial white blood cell count more than 400×10^9/L. Painless enlargement of the scrotum can be a sign of testicular involvement and generally seen in infants with ALL and T cell ALL with hyperleukocytosis. Bone pain may result from infiltration of periosteum, bone infarction or expansion of marrow cavity by leukemic cells. Leukemic cells rarely may infiltrate other organs like the eyes, kidneys, skin (leukemia cutis), gastrointestinal tract and lung. Priapism may result from the involvement of sacral roots or from mechanical obstruction of the corpora cavernosa. Between 1% and 2% patients present initially with pancytopenia and ultimately develop acute leukemia 1–9 months after onset of symptoms. T-acute lymphoblastic leukemia (T-ALL) represents approximately 15% of ALL and usually has distinctive clinical features such as occurrence in older boys, high initial leukocyte count and presence of extramedullary disease like a mediastinal mass and CNS leukemia at diagnosis (10–15%). Infant ALL accounts for 2–5% of childhood leukemias.

Infants usually have a high incidence of poor prognostic factors like high initial white blood count, massive organomegaly, thrombocytopenia, CNS leukemia and failure to achieve remission. The leukemic cells are usually CD19-positive (CD19+) and CD10-negative (CD10–) and CD10+ for MLL rearrangement. Infants need intensive therapy to attain remission and have an event-free survival at 5 years of approximately 40%. Adolescents with ALL frequently present with adverse prognostic factors but have a low rate of favorable genetic abnormalities and have a less favorable outcome than children aged 1–9 at diagnosis with an event-free survival of 73% at 5 years.

DIAGNOSIS

Anemia, neutropenia and thrombocytopenia are common in patients with newly diagnosed patients. The severity reflects the degree of marrow replacement by leukemic lymphoblasts. Higher hemoglobin indicates a more rapidly proliferating leukemia. Hyperleukocytosis ($> 100 \times 10^6$/L) is seen in 10–16% of patients. Profound neutropenia is found in 20–40% of patients rendering them at risk of infection. Patients with the t(5,14) may present with eosinophilia. Severe bleeding is uncommon even when platelet count is less than 20×10^6/L. Mild coagulopathy may be seen in T-ALL; however, it is rarely associated with bleeding. High levels of serum lactate dehydrogenase (LDH) and serum uric acid correlate with high leukemic burden. Serum immunoglobulin (mostly IgA and IgM) are moderately decreased in approximately one-third of patients. Patients with renal involvement especially T-ALL can present with increased levels of creatinine, blood urea nitrogen (BUN), uric acid, phosphorus and can present with acute renal failure. Rarely, patients present with hypercalcemia resulting from release of parathyroid-like protein from lymphoblasts and leukemic infiltration of bones. A complete blood count, coagulation, renal, liver parameters, LDH, uric acid and bone profile is essential at diagnosis. Ultrasonography can diagnose testicular involvement in patient with painless enlargement of scrotum. Chest radiography
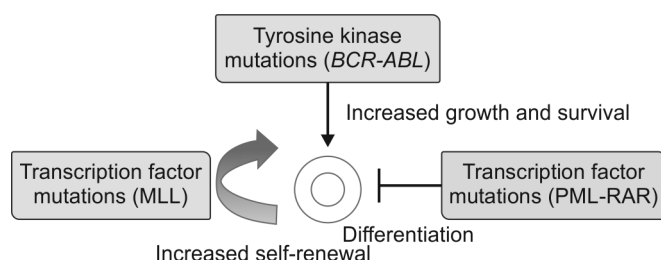
Table 1 Clinical and laboratory presenting features of acute lymphoblastic leukemia (ALL)

Characteristic by immunotype	C-ALL number (%)	T-ALL number (%)	Null number (%)	Total number (%)
Number of patients	335 (68.6)	101 (20.7)	52 (10.7)	530
Age (in years)				
1–< 2	12 (3.6)	2 (2.0)	1 (1.9)	17 (3.2)
2–9	211 (63.0)	38 (37.6)	23 (44.2)	303 (57.2)
10–17	86 (25.7)	49 (48.5)	24 (46.2)	164 (30.9)
18–24	26 (7.8)	12 (11.9)	4 (7.7)	46 (8.7)
Sex				
Male	217 (64.8)	79 (78.2)	35 (67.3)	361 (68.1)
Female	118 (35.2)	22 (21.8)	17 (32.7)	169 (31.9)
WBC (per mm^3)				
< 10,000	135 (40.3)	21(20.8)	19 (36.5)	200 (37.7)
10,000–50,000	132 (39.4)	28 (27.7)	20 (38.5)	192 (36.2)
> 50,000	68 (20.3)	52 (51.5)	13 (25.0)	138 (26.0)
Platelet count (per mm^3)				
< 10,000	12 (3.6)	7 (6.9)	1 (1.9)	22 (4.2)
10,000–100,000	279 (83.3)	74 (73.3)	42 (80.8)	427 (80.6)
> 100,000	44 (13.1)	20 (19.8)	9 (17.3)	81 (15.3)
Hemoglobin (g/dL)				
≤ 6.0	92 (27.5)	20 (19.8)	19 (36.5)	143 (27.0)
> 6.0– ≤ 8.0	101 (30.1)	24 (23.8)	16 (30.8)	150 (28.3)
> 8.0	124 (42.4)	57 (56.4)	17 (32.7)	237 (44.7)
LDH (IU/mL)[a]				
< 500	32 (11.3)	9 (9.9)	5 (10.6)	51 (11.2)
500–1000	125 (44.2)	17 (18.7)	10 (21.3)	170 (37.3)
> 1000	126 (44.5)	65 (71.4)	32 (68.1)	235 (51.5)
Lymphadenopathy	257 (76.7)	93 (92.1)	35 (67.3)	417 (78.7)
Hepatosplenomegaly	270 (80.6)	89 (88.1)	39 (75.0)	424 (80.0)
Mediastinal mass	5 (1.5)	33 (32.7)	1 (1.9)	41 (7.7)
CNS[b] involvement	2 (0.6)	4 (4.0)	0	7 (1.3)
Median height for age[c,d]	170(50.9)	40 (39.6)	23 (44.2)	252 (47.6)
Median weight for age[c]	114 (34.0)	30 (29.7)	13 (25.0)	166 (31.3)
Median height and weight for age[c,d]	89 (26.6)	25 (24.8)	11(21.2)	133 (25.1)

Immunophenotyping was performed on 488 patients
[a] LDH was obtained in 421 patients of those with immunophenotyping results.
[b] CNS involvment was defined as CSF pleocytosis and/or cranial nerve palsies.
[c] Number of patients above the median (50th percentile).
[d] Height data available for 529 patients.

Source: Advani S, Pai S, Venzon D, et al. Acute lymphoblastic leukemia in India: an analysis of prognostic factors using a single treatment regimen. Ann Oncol. 1999;10:167-76.

is needed to assess mediastinal mass especially in T-ALL. Skeletal radiography shows metaphyseal banding, periosteal reactions, osteolysis, osteosclerosis and osteopenia but has no prognostic significance in management. Computed tomography (CT) chest should be done in case of suspected superior mediastinal syndrome and CT spine in patients with suspected vertebral collapse.

Examination of cerebrospinal fluid (CSF) is needed to rule out CNS leukemia. CNS leukemia is defined by presence of more than 5 WBCs/mm^3 and identification of blasts in cytocentrifuged sample or by presence of cranial nerve palsies. A traumatic lumbar puncture at diagnosis (> 10 erythrocytes/μL) is associated with an increased risk of relapse and indicates an overall poorer outcome. CNS involvement is classified as follows:

- CNS 1: < 5 WBCs/mm^3 with no blasts on cytocentrifuged slide
- CNS 2: < 5 WBCs/mm^3 with blasts on cytocentrifuged slide
- CNS 3: > 5 WBCs/mm^3 with blasts on cytocentrifuged slide.

DIFFERENTIAL DIAGNOSIS

The initial manifestations of ALL can mimic a variety of diseases shown in **Box 1**.

CLASSIFICATION

Bone marrow aspiration is essential for the diagnosis for ALL because 10% patients lack circulating blasts at the time of diagnosis and also for genetic studies. Acute leukemia can be classified based upon: (1) morphologic and cytochemical analysis; (2) immunologic classification; and (3) genetic classification (cytogenetic and molecular).

Morphologic and Cytochemical Classification

Morphologic analysis of Romanowsky stained bone marrow films is the first step in diagnosis of ALL. ALL can be further subclassified

based upon French-American-British (FAB) classification as L1, L2 and L3 morphology **(Figs 2 to 4)**. However, because of the lack of independent prognostic significance and the subjective nature, it is no longer used. L3 morphology expresses surface immunoglobulin on their cell surface (mature B-ALL or Burkitt leukemia). The cytochemical stains needed to differentiate between ALL and acute myeloblastic leukemia (AML) are Sudan black, myeloperoxidase
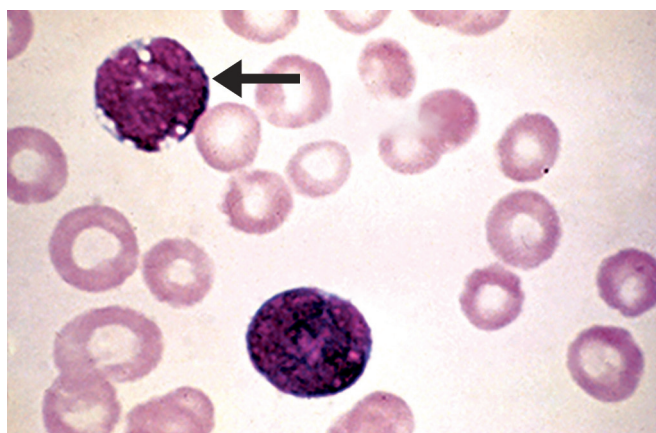
Figure 2 Morphology of acute lymphoblastic leukemia. ALL L1 [French-American-British (FAB) classification]—lymphoblasts are usually smaller with scanty cytoplasm and inconspicuous nucleoli
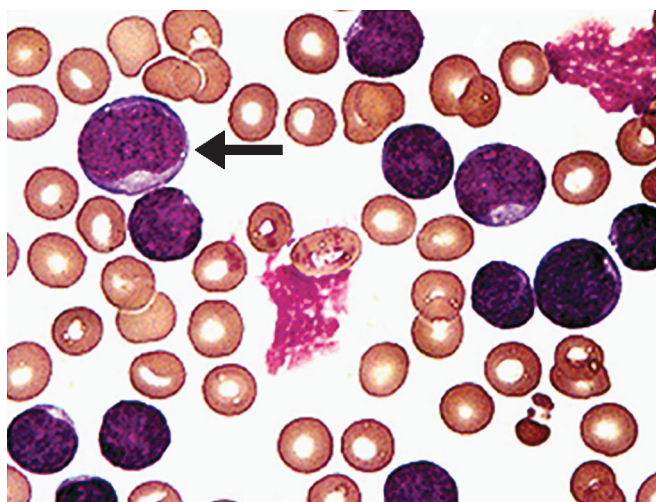
Figure 3 Morphology of acute lymphoblastic leukemia. ALL L2 [French- American-British (FAB) classification]—lymphoblasts are larger, heterogeneity in size, prominent nucleoli and more abundant cytoplasm

and nonspecific esterase (NSE). Staining with periodic acid-Schiff reagent (PAS) is positive in more than 70% of ALL, whereas acid phosphatase can be positive in T-ALL.

Immunologic Classification

Immunophenotyping of leukemic lymphoblasts by flow cytometry is essential to establish the correct diagnosis and define cell lineage. Based upon the immunophenotyping of lymphoblasts, ALL can be subclassified to pre-B-ALL, mature B-cell ALL and T-cell ALL and helps us plan therapy **(Table 2)**. Myeloid-associated antigens (CD13 and CD33) can be expressed in lymphoblasts in about 5–30% of childhood ALL. Although it has no prognostic significance in risk stratification, it can be used for monitoring in minimal residual disease (MRD). Less than 5% of cases of acute leukemia are of ambiguous lineage, expressing features of both myeloid and lymphoid lineage.

Genetic and Molecular Classification

Chromosomal abnormalities are common in childhood ALL. Although not specifically used for diagnosis, cytogenetic findings based upon both the chromosomal numerical and structural abnormalities (gene rearrangement and translocation) are an essential part of the risk group stratification of childhood ALL and help to guide therapy. Standard karyotype analysis is complemented by molecular analysis of known predictive chromosomal abnormalities using fluorescence in situ hybridization (FISH) and other molecular techniques. Cytogenetic findings that affect risk group stratification include t(12,21) ETV6-RUNX1, trisomies of chromosomes 4, 10 and 17, t(9;22) *BCR-ABL*, hypodiploidy and the MLL translocation **(Table 3)**. Hyperdiploidy (> 50 chromosomes) and ETV6-RUNX1 are associated with favorable outcome whereas *BCR-ABL*, MLL translocation, iAMP21, and t(17;19) and hypodiploidy are associated with poor outcome **(Fig. 5)**.

RISK STRATIFICATION IN CHILDHOOD ALL (TABLE 4)

The backbone of current treatment protocols for ALL in children is risk-adapted therapy in order to reduce toxicity in low-risk patients while ensuring appropriate, more aggressive therapy for those with a high risk of relapse. The commonly used criteria are as follows:
• Clinical factors   : Age at diagnosis and initial white blood count
• Biological factors   : Cytogenetics and immunophenotype
• Response to treatment : Clearance of blasts with steroids.
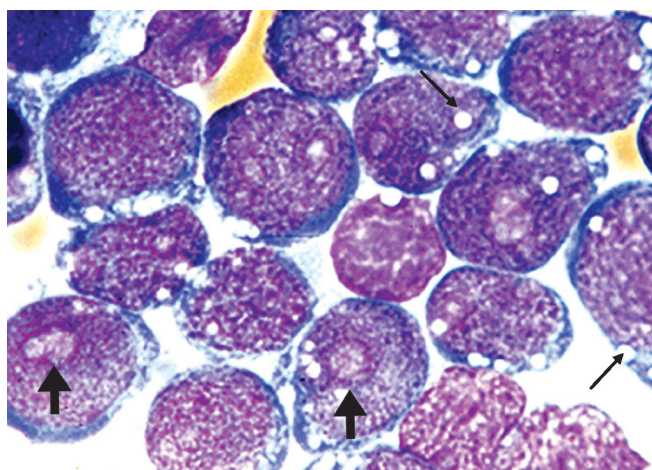
Figure 4 Morphology of acute lymphoblastic leukemia. ALL L3 [French-American-British (FAB) classification]—lymphoblasts have prominent cytoplasmic vacuolation (thin arrows) and their nuclei have prominent nucleoli (bold arrows)

Table 2 Presenting features of acute lymphoblastic leukemia according to immunologic subtype

Subtype	Typical markers	Incidence (%)	Features
B-cell precursor	CD19+, CD22+, CD79a+, sIgμ−, HLA-DR+		
Pre-pre-B (pro)	CD10−, CD19+	5	Infant, high leukocyte count, CNS leukemia, MLL rearrangement, unfavorable prognosis
CALLA+ ALL (early pre-B)	CD10+, cIg−	63	Favorable age group, hyperdiploidy
Pre-B ALL	CD10±, cIg+	16	CNS leukemia, high leukocyte, pseudodiploidy
B-cell	CD19+, CD22+, Cig+, sIgλ+	3	Male predominance, CNS leukemia, abdominal mass, often renal involvement
T lineage	CD7+, Ccd3+		
T-cell (mature)	CD2+, CD4±, CD8±, HLA-DR−, TdT±	12	Male predominance, hyperleukocytosis, extramedullary disease
Pre-T	CD2−, CD1−, CD4−, CD8−, HLA-DR±, TdT+	1	Male predominance, hyperleukocytosis, extramedullary disease, unfavorable prognosis
Early T-cell precursor ALL	CD1a−, CD8− weak expression of CD5, coexpression of stem cell or myeloid markers		Poorer prognosis. Upfront transplantation if persistent MRD-positive

Source: Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med.1998;339:605-15.

Table 3 Clinical and biologic features associated with the most common genetic subtypes of acute lymphoblastic leukemia

Subtype	Associated features	Estimated event-free survival (%)
Hyperdiploidy (> 50 chromosomes)	Predominant B-cell phenotype, low leukocyte count, favorable age group (1–9) years and good prognosis	85–90
Hypodiploidy (< 44 chromosomes)	Predominant B-cell precursor phenotype, increased leukocyte count, poor prognosis	30–40
TEL-AML1 fusion	CD13±/CD33± B-cell precursor phenotype, pseudodiploidy, age 1–9 years, favorable prognosis	85–90
t(1;19)(q23;p13.3) with *E2A-PBX1* fusion	Pre-B phenotype, pseudodiploidy, black race, CNS leukemia	75–90
t(9;22)(q34;q11.2) with *BCR-ABL* fusion	Predominant B-cell precursor phenotype, older age, increased leukocyte count, poor early response to induction or with leukocyte counts > 50×10^9/L	20–40
t(4;11)(q21;23) with *MLL-AF4* fusion	Pro-B phenotype, hyperleukocytosis, CNS leukemia, dismal outcome	10–35
t(8;14)(q24;q32.3)	B-cell phenotype, L3 morphology, male predominance, bulky extramedullary disease, favorable prognosis with short-term intensive chemotherapy	75–85
HOX 11 overexpression	CD10+ T-cell phenotype, favorable prognosis with chemotherapy alone	90

Source: Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350:1535-48.

The projected 5-year event-free survival for low-risk group is above 95% whilst the high-risk groups would be lower than 90%.

MANAGEMENT

The current day management of childhood ALL has come from decades of experience of group trials conducted in different countries. The Children's Oncology Group (COG) from the United States of America, the Berlin-Frankfurt-Münster (BFM) Group from Germany and the UK Medical Research Council (UKMRC) ALL trials have been pioneers in shaping the way we manage childhood ALL today. The broad principles of management include risk stratification on day 1 based on the National Cancer Institute (NCI) criteria, start induction chemotherapy using combination drugs and assess response after 29 days of induction chemotherapy. Based on the day 29 assessment, children are either allocated to downscale treatment schedule, continue on current schedule, escalate chemotherapy, if found to have high risk or are recommended upfront hematopoietic SCT.

On the day of diagnosis, the children are allocated into NCI risk groups based on their age and presenting white cell count as standard risk and high risk to initiate therapy. The chemotherapy schedule includes the following:

- *Induction:* 4 weeks
- *Consolidation:* 4–8 weeks
- *Interim maintenance:* 8 weeks
- *Delayed intensification:* 8 weeks
- *Maintenance:* 2½ years in girls and 3 years in boys.

Induction phase of chemotherapy consists of the use of steroids, vincristine, anthracyclines and asparaginase **(Fig. 6)**. Dexamethasone at 6 mg/m² or prednisolone at 60 mg/m² are the recommended steroids for childhood ALL. This also ensures adequate coverage for sanctuary sites like the CNS where the blasts could escape chemotherapy and relapse at a later date. Long-acting pegylated asparaginase achieves rapid clearance of blasts with less immunological toxicity compared to conventional asparaginase toxicity in the first 29 days. Intrathecal chemotherapy with preservative-free methotrexate is an important component of therapy to prevent CNS disease. Great care must be taken to avoid traumatic lumbar punctures during administration of intrathecal chemotherapy as this increases the chance of a CNS relapse. The
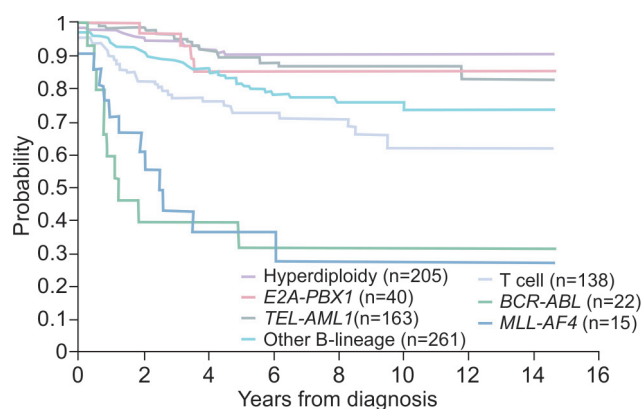
Figure 5 Kaplan-Meier analysis of event-free survival according to biological subtypes of leukemia
Source: Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008;371:1030-43.

Table 4 Contemporary risk stratification of acute lymphoblastic leukemia (ALL) [the Children's Oncology Group (COG)]

Risk category	Criteria
Low risk	Age < 10 years White count < 50,000 Trisomies 4/10, 17, t(12;22), hyperdiploidy Rapid response to therapy with MRD-negative on day 8
Average risk	Age < 10 years White count < 50,000 Cytogenetics other than favorable Slow response to therapy with MRD-positive on day 8 and MRD-negative on day 28
High risk	Age >10 years White count > 50,000 Cytogenetics other than favorable Slow response to therapy with MRD-positive on day 8 and MRD-negative on day 28 CNS positive leukemia Testicular leukemia
Very high risk	MRD-positive on day 29 Age less than 1 (plus above 13 years on COG protocol) Cytogenetics—MLL gene rearrangement or iAMP21 Induction failure
SPECIAL category	T-cell ALL Philadelphia chromosome t(9;22)

Source: Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol. 2009;27:5175-81.

most common side effects seen during induction chemotherapy are mood changes, cushingoid features, hypertension, steroid-induced diabetes and avascular necrosis of femoral head from the prolonged use of steroids, constipation and jaw pain, and occasional syndrome of inappropriate ADH secretion (SIADH) from vincristine, allergic reaction, thrombosis and pancreatitis from asparaginase. Induction mortality can be reduced with effective care and the common causes include sepsis and bleeding.
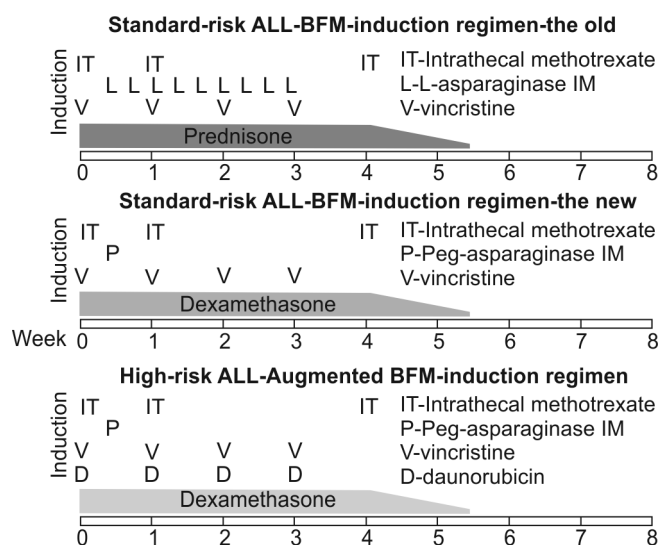
Figure 6 Induction backbone of acute lymphoblastic leukemia (ALL) [Berlin-Frankfurt-Münster (BFM) protocol]

Supportive care has advanced over the past two decades bringing down induction mortality to less than 2% in developed countries. However, this remains the biggest challenge in India as supportive care including blood products, antibiotics and safe environment to administer chemotherapy is expensive, resulting in higher induction mortality of up to 10% in most cancer centers in India.

Consolidation phase involves giving non-cross-resistant chemotherapy drugs such as cyclophosphamide, 6-mercapto-purine (6-MP) or 6-thioguanine (6-TG) with cytarabine **(Fig. 7)**. It helps clear the resistant residual leukemic disease after induction. This is followed by interim maintenance which involves giving intravenous methotrexate either in escalating doses without leucovorin rescue with vincristine or high-dose methotrexate with low-dose 6-MP and intrathecal methotrexate which not only helps in improving the outcome but also helps in clearance of disease from CNS and prevents CNS relapses. Cranial radiotherapy for prophylaxis is now completely removed from most international protocols.

The principles of induction and consolidation chemotherapy are introduced again in delayed intensification phase **(Fig. 8)** so as to ensure eradication of any malignant clone that would have been left behind from the initial 16–20 weeks of chemotherapy.

Maintenance chemotherapy in childhood ALL is for over 2 years in girls and 3 years in boys. It involves daily oral 6-MP and weekly oral methotrexate and 3 monthly vincristine with

Figure 7 Consolidation backbone of acute lymphoblastic leukemia (ALL) [Berlin-Frankfurt-Münster (BFM) protocol]

Delayed intensification for standard risk ALL-BFM regimen

```
Delayed
intensification

IT                    IT      IT
V     V     V         C
D     D     D         AAAA    AAAA
   [Dexamethasone]       [6-thioguanine]
0    1    2    3    4    5    6    7    8
```

Delayed intensification for High risk ALL-BFM Augmented regimen

```
Delayed
intensification

IT    P               IT      IT      P
V     V     V         C               V     V
D     D     D         AAAA    AAAA
   [Dexamethasone]       [6-thioguanine]
0    1    2    3    4    5    6    7    8
      P-Peg-asparaginase; V-Vincristine; D-Doxorubicin
```

Figure 8 Delayed intensification backbone of acute lymphoblastic leukemia (ALL) [Berlin-Frankfurt-Münster (BFM) protocol]

steroids in some protocols **(Fig. 9)**. Mercaptopurine forms the backbone of childhood ALL maintenance therapy. Although an oral preparation, it carries great marrow suppressive potential and blood counts need to be monitored every 2 weeks. Bioavailability is best when administered in the evening without simultaneous milk consumption. The titration of mercaptopurine to allow absolute neutrophil count values between 750/mm³ and 1500/mm³ has shown to improve outcome. Intrathecal chemotherapy with methotrexate every 12 weeks needs to be continued in order to prevent a CNS relapse.

Assessment of Minimal Residual Disease

Minimal residual disease means presence of submicroscopic disease (usually considered significant if greater than 1 in 10,000 leukemic cells) after chemotherapy at any time point. MRD assessment is done on day 19, at the end of induction or week 11 based the type of protocol used. MRD can be assessed by flow cytometry or by polymerase chain reaction (PCR) method and forms the backbone of risk stratification in ALL. MRD less than 0.01% at the end of induction carries over a 95% chance of disease-free survival.

Supportive Care during Chemotherapy

Optimal survival in ALL depends on delivery of optimal supportive care. Blood component support to prevent bleeding, antibiotic support to prevent death from sepsis, clean environment of care during neutropenic periods, clean diet and psychosocial support are known to improve survival in childhood ALL. The children are encouraged to eat well cooked normal home foods and avoid salads and fresh fruits, ensure adequate physical activity in a clean environment and participate in school activities after the intensive chemotherapy period is completed. All vaccines are to be avoided during chemotherapy and advice on how to treat fever during

Maintenance phase

```
IT
V              V              V
IIIII          IIIII          IIIII
M  M  M  M  M  M  M  M  M  M  M  M
          [6-mercaptopurine]
0  1  2  3  4  5  6  7  8  9  10  11  12/0
```

Figure 9 Maintenance backbone of acute lymphoblastic leukemia [Berlin-Frankfurt-Münster (BFM) protocol]

chemotherapy is given on a printed chart with the number of the medical personnel to be contacted for an emergency. All children need to be on prophylactic co-trimoxazole 2 days a week to prevent infection with *Pneumocystis jirovecii*. The response of an individual child to different chemotherapeutic agents is also driven by genetic features and pharmacogenetics is now a rapidly advancing field in oncology necessitating individualized treatment. Hospital infection control policy and empiric broad-spectrum antibiotic use for neutropenic fever based on local antibiotic sensitivity protocol help reduce mortality during induction. Seizures can occur during induction due to hypertension that induces posterior reversible encephalopathy syndrome (PRES), thrombocytopenia resulting in bleed, thrombosis due to asparaginase and CNS involvement. Antiepileptic drugs that do not interact with chemotherapy medications such as levetiracetam are recommended.

Special Categories of ALL

Philadelphia chromosome-positive ALL This group had the worst survival until a decade ago and all patients required SCT. With the introduction of imatinib, a targeted agent to specifically inhibit tyrosine kinase generated from the *BCR-ABL* gene rearrangement, combination chemotherapy with imatinib is now the standard of care and SCT is used in patients with poor response to therapy.

T-cell ALL It is treated as per high-risk protocol with four-drug induction. It is now known that high-dose methotrexate infusions at a dose of 5 g/m² can provide effective antileukemic therapy in T-ALL.

Central nervous system disease CNS disease at presentation is treated with cranial radiotherapy of 18 Gy in addition to chemotherapy. It is now known that delaying cranial radiotherapy until completion of delayed intensification and avoiding mercaptopurine during radiotherapy will help reduce late side effects like second malignancy.

High-risk ALL Children with high-risk cytogenetic categories like hypodiploidy, MLL gene rearrangement, and persistent MRD after consolidation may be offered SCT as per institution policy.

Management of Relapsed ALL

The diagnosis of relapse carries a huge psychosocial impact on the family especially in developing countries as most families do not have insurance cover for their treatment. The time of relapse carries the highest significance. Children who relapse 3 years after the initial diagnosis may be salvage with chemotherapy. Those that relapse between 18 months and 3 years from diagnosis need to be assessed at the end of induction with MRD and counseled. Relapse less than 18 months from diagnosis carries a grave prognosis and a handful of these children can be cured with hematopoietic SCT. MRD-negative state at the time of transplant offers the best chance of cure. Transplantation using total body radiation-based conditioning regimens is toxic and need to be avoided in children less than 3 years of age.

After Therapy Care

Chemotherapy for ALL is over a prolonged period of time. Most children will need vaccination schedules to be completed after chemotherapy. Regular follow-up for relapse is required for the first 2 years. Most institutions recommend monthly blood counts for the first 2 years after completion of treatment or to report back if there are any new symptoms in the child. Cardiac echocardiogram and viral screening to ensure that there have been no side effects

of the treatment are part of end of therapy work-up. Periodic monitoring of growth and development and advice regarding calcium-rich diet and exercise to improve bone strength needs to be conveyed to the shared care pediatrician. Late relapses beyond 5 years of chemotherapy are rare and long-term follow-up in special clinics helps reinforce healthy lifestyle practices.

IN A NUTSHELL

1. Childhood ALL has over 80% cure rates.
2. Immunophenotyping, karyotyping and molecular markers are important at diagnosis.
3. Risk stratification is the key to optimal management.
4. Minimal residual disease assessment has helped guide therapy.
5. Cranial radiotherapy is not recommended for prophylaxis due to late side effects except in selected cases with CNS disease.
6. Imatinib with chemotherapy is used in the Philadelphia chromosome-positive childhood ALL.
7. Hematopoietic SCT is reserved for the children with high-risk disease and those who have relapsed.

MORE ON THIS TOPIC

Advani S, Pai S, Venzon D, et al. Acute lymphoblastic leukemia in India: an analysis of prognostic factors using a single treatment regimen. Ann Oncol. 1999;10:167-76.

David GP, Pizzo PA. Principles and Practice of Pediatric Oncology. 6th ed. USA: Lippincott Williams and Wilkins; 2011. pp. 519-65.

Harrison CJ. Cytogenetics of paediatric and adolescent acute lymphoblastic leukemia. Br J Haematol. 2009;144:147-56.

Lanzkowsky P. Manual of Pediatric Hematology and Oncology. 5th ed. USA: Elsevier; 2011. pp. 518-65.

Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360:2730-41.

Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354:166-78.

Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008;371:1030-43.

Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. J Clin Oncol. 2009;27:5175-81.

Vrooman LM, Silverman LB. Childhood acute lymphoblastic leukemia: update on prognostic factors. Curr Opin Pediatr. 2009;21:1-8.

Chapter 45.3
Acute Myeloid Leukemia
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Acute myeloid leukemia (AML) is a clonal hematopoietic stem cell disease, characterized by proliferation of nonfunctional myeloid precursors called blasts in the bone marrow. Acquired mutations in proliferative and differentiation pathways of myeloid precursor cells cause this maturation arrest and clonal proliferation. The result is impaired normal blood cell production in the marrow, causing cytopenias. Childhood AML, in contrast to acute lymphoblastic leukemia (ALL), has a poorer prognosis. Therapeutic approaches to children with AML have continued to emerge from the largely successful clinical trials from various cooperative groups. Despite the developments, 5-year event-free survival (EFS) in children is only 50–60%. This chapter summarizes our current understanding of pediatric AML with respect to their classification, diagnosis, newer chemotherapeutics and risk-based approach to treat pediatric AML.

INCIDENCE AND RISK FACTORS

Acute myeloid leukemia constitutes only about 15–20% of all leukemias in children younger than 20 years of age. According to data from Surveillance, Epidemiology, and End Results (SEER) of US National Cancer Institute (NCI), the incidence rates of AML have remained constant over the past three decades. There is a bimodal age distribution with highest rates seen in children younger than 2 years, reaching nadir at about 9 years and then again peaking in adolescents 15–20 years old. Incidence rates are equal between boys and girls in all age groups.

In India, according to the data from the Indian Council of Medical Research, National Cancer Registry Programme, of all pediatric cancers in males (0–14 years of age), the incidence of AML ranged from 0% in Ahmedabad registry to 7% in Mumbai and Delhi registry. This constitutes 0–10% of all leukemias. Similar incidence is observed for females as well. The 5-year overall survival (OS), across various periods ranged from 10% in Bengaluru registry to 30% in Chennai to 58% at a tertiary care center like Tata Memorial Hospital in Mumbai.

The cause of AML remains elusive. Majority of children have de novo AML with no identifiable risk factor. In a subset of patients, environmental exposure to carcinogens, inherited predisposition or acquired disorders are associated with the development of AML **(Box 1)**. AML with Down syndrome (DS) is discussed in greater detail later in the chapter.

The environmental carcinogens most directly linked are exposure to ionizing radiation, benzene and chemotherapeutic drugs given for previous cancers. The therapy-related AML (from chemotherapeutic drugs) are of two types: (1) following alkylating agents: this occurs 5–10 years after the exposure to alkylating agents such as cyclophosphamide, ifosfamide, and is usually preceded by myelodysplasia. The typical cytogenetic abnormality is monosomy of chromosome 5 or 7; and (2) following topoisomerase II inhibitors: the AML which develops after exposure to agents such as etoposide and anthracyclines has a shorter latency period of 1–3 years and is less often associated with myelodysplasia. The typical cytogenetic abnormality is a balanced translocation involving band 11q23.

DIAGNOSIS

Clinical Features

Children with AML can present with exceptionally varied symptoms and signs. These manifestations result mainly from one or a combination of following factors: arrest of normal hematopoiesis with bone marrow infiltration by leukemia cells, extramedullary tissue invasion and leukostasis.

Bone marrow infiltration by leukemic blasts leads to pancytopenia, although the total white blood cell (WBC) count is generally elevated. The patients may present with fever, fatigue, pallor, bleeding, bone pain, infections and disseminated intravascular coagulation (DIC). Infiltration of extramedullary sites can result in lymphadenopathy, hepatosplenomegaly, chloromatous tumors (myeloid sarcomas), leukemia cutis, gingival hypertrophy, infiltration of orbit, epidural space and, rarely, testicular involvement. Such extramedullary involvement is more common in M4 and M5 subtypes and in infants. Chloromas and central nervous system (CNS) diseases are more common in AML with t(8,21) translocation. Patients who have high WBC counts may present with signs or symptoms of leukostasis, most often affecting the lungs and brain and needs urgent intervention.

A complete blood count usually shows a high WBC count with low circulating granulocytes, although a low WBC count can also occur occasionally. The median WBC count at diagnosis is approximately 20×10^9/L (0.3–28000×10^9/L). Higher count is more common in patients with M4 and M5 subtypes. A normocytic anemia is common and the platelet count is almost always decreased. DIC has been reported in all subtypes of AML but is particularly seen in acute promyelocytic leukemia (APL). Peripheral blood smear should be reviewed systematically for blasts, blast equivalents, other abnormal cells, and dysplasia (all hematopoietic lineages). Asymptomatic CNS is common—may occur in up to 15% of cases.

French-American-British Classification

The French-American-British (FAB) classification takes into account the morphologic, cytochemical and immunophenotypic criteria to define eight subtypes (M0–M7) of AML and has evolved over the years. Some of the salient features of various FAB/WHO subtypes are listed in **Table 1**. Currently a modified WHO classification is used and includes cytogenetics which is depicted in **Box 2.**

Morphology and Histochemistry

Morphologic examination of bone marrow aspirate smears with cytochemical staining is the method used to identify subtypes of AML and forms the basis for the FAB classification system.

BOX 1 Predisposing factors for the development of acute myeloid leukemia

Environmental
- Chemotherapy (alkylators and topoisomerase II inhibitors)
- Pesticides
- Petroleum products
- Ionizing radiation

Inherited
- Down syndrome
- Fanconi anemia
- Kostmann syndrome
- Shwachman-Diamond syndrome
- Diamond-Blackfan syndrome
- Dyskeratosis congenita
- Congenital amegakaryocytic thrombocytopenia
- Ataxia-telangiectasia
- Klinefelter syndrome

Acquired
- Aplastic anemia
- Myelodysplastic syndrome
- Paroxysmal nocturnal hemoglobinuria

The myeloid nature of blasts can be established with the Wright-Giemsa stain by presence of granulated blasts, Auer rods and myelodysplasia, in some cases. Immunohistochemistry (IHC) helps confirm the morphology findings. The stains mostly used to identify AML blast are myeloperoxidase (MPO), Sudan black B (SBB) and esterase stains. However, at present immunophenotyping has supplanted the use of IHC.

Immunophenotyping

Immunophenotyping by flow cytometric analysis remains the mainstay of diagnosis. The distinctive immunophenotypic features are also useful in the assessment for minimal residual disease (MRD). Antigens frequently used for myeloid lineage assessment are cytoplasmic myeloperoxidase (cMPO), CD13, CD33 and the stem cell marker CD34. MPO remains the most specific marker of myeloid differentiation and is required for the diagnosis of AML. The anti-MPO test by flow cytometry is more sensitive than the cytochemical stain for MPO and cases of AML which are negative for MPO (AML-M0) by IHC are positive with anti-MPO on flow cytometry. Other markers related to lineage differentiation include CD14 and CD11b in AML-M4 and M5, glycophorin A in AML-M6 and platelet glycoproteins CD41, CD42 and CD61 in AML-M7 **(Table 1)**.

Cytogenetics

Approximately 50% of children with AML will have chromosomal abnormalities identified by conventional cytogenetics or fluorescence in situ hybridization (FISH). Specific chromosomal changes have been linked to certain FAB subtypes notably t(15;17) in APL; t(8;21) and t(6;9) in M2 AML and inv16 with acute monocytic leukemia with increased eosinophils in the marrow—AMLEo or M4Eo. Cytogenetic abnormalities correlate strongly with age with 50% of infants have mixed lineage leukemia or *MLL* gene rearranged AML, whereas core-binding factor (CBF) AML occurs typically in older children (see here). Cytogenetics represents the single most important prognostic factor in predicting remission rate, relapse risks, and OS. Based on cytogenetics, three risk groups have been identified for treatment risk stratification and the 5-year survival rates for those with favorable, intermediate-risk, and poor-risk cytogenetics are 65%, 41%, and 14%, respectively.

Favorable Cytogenetics

The t(8;21) causing *AML1-ETO* fusion gene and inv(16) causing *CBFB-MYH11* fusion are two of the most commonly identified translocations in pediatric AML and are often referred to as CBF leukemias. Approximately 17% of the pediatric patients have CBF leukemia [12% with t(8;21) and 5% with inv(16)]. Patients with t(8;21) and inv(16) have significantly better OS (5-year OS, 69% and 61% respectively) than patients with the normal karyotype.

Intermediate Cytogenetics

A rearrangement of the *MLL* gene, located at chromosome band 11q23 is seen in as many as 20% of cases of pediatric AML, although the reported frequency varies. Among those patients, who had t(9;11) had a better prognosis (5-year EFS estimate, 65%) as compared to patients with other *MLL* rearrangements.

Table 1 FAB classification of acute myeloid leukemia (AML)

FAB subtype	Morphology and histochemistry	Flow cytometry	Cytogenetics	Comments
M0	• Poorly differentiated AML • Hypercellular marrow with > 90% blasts • MPO < 3%	• Anti-MPO, CD13+, CD33+, CD34+ • Absence of lymphoid and megakaryocytic markers	Complex cytogenetics	• 1–5% of pediatric AML • Poor prognosis
M1	• Hypercellular marrow • Myeloblastic without maturation • MPO > 3%	• Anti-MPO, CD13+, CD33+, CD34+	Monosomy 5, 7 or trisomy 8	• 10–15% of pediatric AML • Average prognosis
M2	• Myeloblast with maturation • Represent more than 30% of bone marrow cells • Presence of Auer rods • MPO and SBB+	• Anti-MPO, CD13+, CD33+, CD34+, HLA-DR+	t(8,21)(q22;q22)	• 20–25% of pediatric AML • Increased chloromas
M3	• Abnormal promyelocytes • Auer rods common • A hypogranular variant (M3v) • Strongly MPO and SBB+	• Anti-MPO, CD13+, CD33+, CD11+, HLA-DR–, CD34–	t(15,17) (q24;q21)	• 3–15% of pediatric AML • Associated coagulopathy • Favorable prognosis with ATRA
M4	• Myelomonocytic • Monocytic component > 20% but < 80% of leukemic cells • M4E0 associated with > 5% abnormal eosinophils	• Myelomonocytic markers CD13, CD33, CD4, CD11b, CD14, CD15, CD64, HLA-DR	Inv16 or t(16,16) (p13;q22)	• 15–30% of pediatric AML • Favorable prognosis
M5	• At least 80% of leukemic cells are monoblasts • Intense NSE activity, MPO-negative	• Monocytic markers such as CD11b, CD14, CD15, CD64, HLA-DR	Translocations involving *MLL* gene at 11q23 locus	• 15–20% of pediatric AML • Hyperleukocytosis, DIC, extramedullary disease
M6	• Erythroleukemia with erythroblast > 50% of total nucleated cells	• Glycophorin A+	Monosomy 5 or 7 or trisomy 8	• 1–3% of pediatric AML • Poor prognosis
M7	• Megakaryocytic • Associated with marrow fibrosis • MPO-negative	• Platelet peroxidase+ by electron microscopy • CD41+, CD61+	t(1,22)(p13;q13) in non-DS	• 4–10% of pediatric AML (mostly infants) • Most common in DS • Unfavorable prognosis (except in DS)

BOX 2	Current WHO classification of acute myeloid leukemia (AML) (WHO 2008)

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1 (CBFα/ETO)*
  - AML with inv(16)(p13;q22) or t(16;16)(p13;q22), *CBFβ-MYH11*
  - Acute promyelocytic leukemia with t(15;17)(q22;q11-12), *PML-RARα*
  - AML with t(9;11)(p22;q23), *MLLT3-MLL*
  - AML with t(6;9)(p23;q34); *DEK-NUP214*
  - AML (megakaryoblastic) with t(1;22)(p13;q13), *RBM15-MKL1*
  - AML with mutated *NPM1*
  - AML with mutated *CEBPα*

- AML with myelodysplasia-related features
- Therapy-related myeloid neoplasms
- AML, not otherwise specified
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic and monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

Adapted from: Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5);937-51.

Unfavorable Cytogenetics

Monosomy 7, monosomy 5/5q deletions, and aberrations of 12p, seen in 3–5% of patients, are associated with poor outcome. Patients with monosomy 7 have particularly worse outcome with 5-year OS 30%.

Molecular Markers

Significant advances in the molecular diagnostic techniques are yielding new inputs for the treatment of cytogenetically normal pediatric AML. Several of these mutations having prognostic importance are described in recent clinical trials. Some relevant to pediatric AML are discussed here.

FLT3 mutations [internal tandem duplication (ITD) and activating loop mutation (ALM)] FLT3/ITD has a prevalence of 12–15% in pediatric patients, 20–25% in young adults and nearly 35% in the elderly population. FLT3 mutations confer a worse prognosis. Stem cell transplant (SCT) might improve outcome in children with FLT3/ITD-positive AML.

C-kit mutations C-kit mutation occurs in about 25% of CBF leukemias. The prognostic significance of these mutations remains unclear. The Japanese Childhood AML Cooperative Study Group found C-kit mutations (8 of 46 children) with t(8;21) were associated with significantly worse OS, disease-free survival (DFS), and relapse rates. Other studies did not support these findings.

Nucleophosmin 1 (NPM1) NPM mutations have been reported in 30–50% of adult patients but in only 10% of children. Although, considered to be favorable, evaluation of the prognostic significance of NPM mutations in children with AML treated in one North American trial failed to demonstrate any prognostic significance for this mutation in pediatric AML.

CCAAT/enhancer binding protein-alpha (CEBPα) The prevalence of CEBPα mutations in pediatric AML is somewhat lower as compared to adults (< 10%). Phoenix Ho et al. evaluated prognostic significance of CEBPα mutations in 847 children with AML treated on three consecutive pediatric trials. Actuarial EFS at 5 years was 70% versus 38% (P = 0.015) with a cumulative incidence of relapse from complete remission (CR) of 13% versus 44% (P = 0.007) for those with and without biallelic CEBPα mutations.

PROGNOSIS

In spite of remarkable advances in the field of diagnosis and treatment of pediatric AML, the survival of these patients is not more than 50–60%. Present definitions of risk groups in AML combine cytogenetic and molecular information **(Table 2)**. Aside from the cytogenetics and molecular risk factors, response to therapy is one of the strongest predictor of outcome. The prognostic value of MRD by flow cytometry was well demonstrated by the Children's Oncology Group (COG) and St. Jude AML studies where children with MRD levels of 1% or higher after one course of induction had significantly lower survival rate compared to those with undetectable MRD.

APPROACH TO DIAGNOSIS

Acute myeloid leukemia is suspected based on clinical and laboratory features and confirmed by identification of myeloblasts. The minimal diagnostic requirements are morphology with cytochemistry, immunophenotyping, karyotyping and FISH. Specific molecular genetics, if available, should also be performed on bone marrow blasts. These tests may be done on peripheral blood in those with high blast counts and if the patient's condition contraindicates a bone marrow aspirate. Unlike in adults, a lumbar puncture is necessary in children, as a part of initial investigation due to higher (about 10–15%) incidence of CNS involvement. However, in a bleeding or unstable patient (new APL cases), lumbar puncture should be deferred until the patient is stabilized.

The diagnosis of AML is generally made when at least 20% of the cells in the blood or bone marrow are blasts of myeloid origin but it is not mandatory. The WHO 2008 classification, includes clinical and biological features, morphologic findings (FAB subtypes), immunophenotypic and cytogenetic features to define specific disease entities **(Box 2)**.

Table 2 Risk status based on cytogenetics and molecular abnormalities

Risk status	Cytogenetics + Molecular markers
Better risk	• Inv(16) or t(16,16) t(8,21) [core-binding factor (CBF) leukemias] • Normal cytogenetics: with NPM1 mutation or isolated CEBPα mutation in the absence of FLT3-ITD • APL-t(15,17)
Intermediate risk	• Cytogenetics—normal (CGN leukemias) • +8 • (9,11) • CBF leukemias with c-kit mutations • Other nondefined
Poor risk	• CGN leukemias with FLT3-ITD mutation • Complex (> 3 chromosomal abnormalities) • -5, 5q-, -7, 7q- • 11q23, non-t(9,11) • t(6,9) • t(9,22)

Adapted and modified from NCCN guideline for AML.

MANAGEMENT

Pediatric AML is a complex and life-threatening disease, and optimal facilities are required for its diagnosis, treatment and follow-up. These patients should be treated in well-equipped pediatric oncology centers, on pediatric protocols. The treatment should be risk-adapted, to improve outcome and to minimize the morbidity and mortality associated with the therapy. Special attention should be given to supportive care such as prevention and treatment of tumor lysis syndrome, hyperleukocytosis, and infection complications. Treatment of AML has been largely divided into induction chemotherapy and postremission (or consolidation) therapy. Therapeutic approaches have continued to emerge from several well-designed trials by various cooperative groups. AML in DS children and APL are distinct entities and the treatment strategy is different in these two settings. Below is general description of the common AML variants.

Induction Therapy

The primary goal of induction therapy is to achieve a significant reduction of leukemia burden, i.e., achievement of morphological CR (clinical remission). One or two courses of induction are usually used. The standard induction therapy consists of a combination of cytarabine and an anthracycline in a 7 + 3 strategy. That is, cytarabine (typically 100 mg/m^2/day) administered by continuous infusion over 7 days with an anthracycline (daunorubicin 45–60 mg/m^2 given on days 1–3). Several strategies have been tried to achieve further intensification of this regimen, such as increasing the dose of cytarabine, prolonging the time of administration or early administration of subsequent courses of therapy. All three approaches have been explored in phase III trials in children. The Pediatric Oncology Group (POG) compared high-dose cytarabine (1 g/m^2) to standard-dose cytarabine in 3 + 7 regimen. It failed to improve response rate or EFS. The Children's Cancer Group (CCG) reported that intensively timed induction therapy (the second cycle delivered 10 days instead of 14 days after the first cycle) was more advantageous than standard therapy (significantly higher CR and EFS rates). Intensification by protracted cytarabine administration (over 8–10 days) is favored by UK cooperative group. Certain anthracyclines (idarubicin and mitoxantrone) are favored for their perceived greater antileukemic effect and/or lower cardiotoxicity, but no anthracycline agent has been demonstrated to be superior. Addition of a third drug to the 7 + 3 regimen has not been shown to be beneficial.

Postremission Therapy

The current recommendation is to employ risk-based consolidation therapy in pediatric AML. For low-risk patients, two to five courses of combination chemotherapy with high-dose cytarabine, anthracycline with or without the addition of a third drug such as etoposide or 6-thioguanine are used to consolidate and maintain remission. For high-risk patients, hematopoietic stem cell transplant (HSCT) is recommended postinduction in first CR as consolidation therapy (see here). Intermediate-risk patients are generally consolidated with two to five courses of chemotherapy or HSCT if a matched sibling is available. The role of allo-HSCT in intermediate-risk patients is less clear.

Maintenance Therapy

The benefit of maintenance therapy in children when tested in randomized trials has shown controversial results. As remission and postremission consolidations have intensified, maintenance therapy has been omitted or abbreviated by most groups. In patients who have non-APL AML, maintenance treatment showed no benefit in randomized studies; these studies even suggested that maintenance therapy may be deleterious. Thus, maintenance therapy is not employed in non-M3 AML treatment.

CNS-Directed Therapy

The incidence of asymptomatic CNS involvement is high in AML (10–15% in various studies) but the incidence of CNS relapse is low. The risk factors for a CNS relapse in AML are not as clear as in ALL, but include CNS involvement at initial diagnosis, hyperleukocytosis at presentation and monocytic AML. Thus, CNS prophylaxis is recommended for all children. High-dose cytarabine, given systemically, crosses blood brain barrier and is an effective CNS prophylaxis but is not adequate in itself. The adequate prophylaxis usually consists of four to five doses of intrathecal chemotherapy with either cytarabine or methotrexate or a combination of these two with hydrocortisone given concurrently with systemic chemotherapy. Cranial irradiation is reserved for patients with overt CNS involvement at the time of diagnosis.

Supportive Care and Control of Infections

The treatment is intensive and prolonged neutropenia is common with virtually all courses of therapy. There is associated high mortality from infections—bacterial and fungal. With high-dose Ara-C regimens, there is a particular increase in α-streptococcal infection. Prompt initiation of antibiotics directed at both gram-negative bacilli and gram-positive α-streptococci is crucial in salvaging the patients—a common regimen is to initiate therapy with cefepime and vancomycin. In some recent trials, prophylactic cefepime/ciprofloxacin drastically reduced death from α-strepto-coccal infections. Benefit from prophylactic antifungals is less clear.

Current Status of Stem Cell Transplant

The role of both autologous and allogeneic SCT has been explored in the treatment of pediatric AML. Auto-SCT does not provide a survival advantage over intensive chemotherapy, and it may not be superior to nonmyeloablative chemotherapy. Thus, auto-SCT is not recommended for children with AML in first CR. The role of allogeneic SCT, particularly whether it should be done during first CR or reserved for second remission, remains the most controversial issue in pediatric AML. Most groups agree that children with favorable risk features, such as those who have APL, AML and DS or AML with t(8;21) or inv(16), are not candidates for SCT in first CR. For intermediate-risk patients, a significant benefit in DFS and OS was found in children treated with allogeneic SCT. Benefit from allogeneic bone marrow transplantation (allo-BMT) is less certain for high-risk patients, although it is a common practice to offer allo-BMT in first CR for these patients because of low second CR rates. The risks for treatment-related morbidity and mortality remain high from unrelated donors with less than perfect match.

As newer strategies of risk stratification, based on MRD analysis and molecular markers, redefine the role of allo-SCT in intermediate-risk group, some patients with low MRD at the end of induction and no unfavorable molecular markers may be treated with chemotherapy alone.

Table 3 Novel agents for acute myeloid leukemia

Drug class	Agents	Mechanism of action
Immunotoxins	Gemtuzumab, Ozogamicin	CD33 binding, toxin internalization, and double-strand DNA breaks
Monoclonal antibodies	Lintuzumab	CD33 binding, complement-dependent cytotoxicity, and antibody-directed cellular cytotoxicity
Newer nucleoside analogs	Clofarabine, Troxacitabine, Sapacitabine	Inhibition of ribonucleotide reductase and DNA polymerase; induction of apoptosis
Hypomethylating agents	Azacitidine, Decitabine	Inhibition of DNA methylation
Farnesyltransferase inhibitors	Tipifarnib, Lonafarnib	Inhibition of farnesyltransferase, inhibition of angiogenesis, and induction of cellular adhesion
Alkylating agents	Laromustine	DNA alkylation and DNA cross-linking
FMS-like tyrosine kinase 3 (FLT3) inhibitors	Lestaurtinib, Tandutinib	Inhibition of FLT3 phosphorylation, induction of apoptosis
Multidrug-resistant modulators	Valspodar, Zosuquidar	Binding to P-glycoprotein and inactivation of its efflux function

Newer Chemotherapeutics and Targeted Agents

Given the poor prognosis and the severe toxicity associated with the current chemotherapeutic agents, there is an unmet need to develop newer novel agents for the treatment of pediatric AML. Cytarabine and anthracycline such as daunorubicin or idarubicin remain the gold standard for the treatment of AML in all age groups. Many new agents with diverse putative mechanisms of action are currently entering clinical trials for adults **(Table 3)**.

Minimal Residual Disease Monitoring

The role of detection of disease below the level of morphological remission in the treatment of pediatric AML is once again following the footprints of treatment of ALL. With more and more data evolving, the role of MRD monitoring as a prognostic marker is being defined slowly. In one study, patients who were in morphologic CR, but had evidence of disease by flow cytometric analysis (MRD-positive), had a fivefold higher risk for relapse than the MRD-negative patients, with a relapse-free survival (RFS) rate from remission of 35%, compared with 65% for the MRD-negative patients. In a multivariate analysis, flow cytometric detection of MRD showed the strongest correlation with RFS.

AML IN SPECIAL CIRCUMSTANCES

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia or AML-M3 represents less than 10% of childhood AML. It is characterized by the presence of a balanced reciprocal translocation between the long arms of chromosomes 15 and 17 [t(15;17)(q22;q21)] which is seen in 98% of cases. It causes a block in differentiation and accumulation of abnormal promyelocytes in bone marrow. APL patients at presentation have a lower WBC as compared to other pediatric AML subtypes. There is a higher incidence of coagulopathy such as DIC, i.e., often worsened by chemotherapy. A microgranular variant of APL, M3v, is associated with a higher WBC and more severe bleeding. Treatment of APL is distinct from therapy of other subtypes. Supportive measures to counteract the coagulopathy should be instituted immediately the diagnosis of APL is considered. All-trans retinoic acid (ATRA) is the mainstay of therapy. ATRA restores normal myeloid maturation by overcoming the promyelocytic leukemia-retinoic acid receptor-alpha (PML-RARα)

induced blockade of RAR. Treatment with ATRA should be initiated without waiting for genetic confirmation of the diagnosis, preferably the same day that diagnosis is suspected, since it decreases the risk of severe bleeding. The current standard in APL is the combination of chemobiological treatment consisting of ATRA + anthracyclines ± cytarabine induction followed by consolidation with ATRA + chemotherapy then maintenance with ATRA + chemotherapy for up to 2 years. Arsenic trioxide (ATO) has also shown promising results in both relapsed and newly diagnosed APL. This agent has been shown to be particularly effective in newly diagnosed children with APL by decreasing the rate of complications, hospital stay and thus overall cost of treatment. Combined therapy with ATRA and ATO is emerging as the current favored treatment approach.

AML with Down Syndrome

Down syndrome children have a 10- to 20-fold higher risk for developing ALL and AML, as compared with non-DS children. DS children with leukemia frequently experience higher levels of treatment-related toxicity and inferior EFS rates, as compared with non-DS children. DS children also develop AML with unique features and have a 600-fold increased risk of developing the AML subtype, acute megakaryocytic leukemia (AMkL; M7). Nearly 10% of DS newborns are diagnosed with a variant of AMkL, the transient myeloproliferative disorder (TMD), which can resolve spontaneously without treatment; EFS rates for DS patients with AMkL range from 80% to 100%, in comparison with less than 30% for non-DS children with AMkL. Somatic mutations of the *GATA1* gene have been detected in nearly all DS TMD and AMkL cases but not in leukemia cases in non-DS children. The high EFS is related, in part, to increased sensitivity of DS megakaryoblasts to cytarabine and daunorubicin. In children with DS, there is a delicate balance between the antileukemic efficacy of intensive chemotherapy and the increased toxic morbidity and mortality rates. The current goals of treatment are to achieve same high rate of remission induction and EFS with less intensive therapy than is required for children with AML without DS.

Relapsed AML

There is currently no uniform approach to treatment of relapse, but most study groups believe that cure without allogeneic SCT is impossible. After relapse, the survival rate is only 20–30%

as per recent reports. Various remission induction regimens, including the FLAG regimen [fludarabine plus cytarabine and granulocyte colony-stimulating factor (G-CSF)] with idarubicin, or mitoxantrone and cytarabine, seem to give similar results. The targeted immunotherapy agents such as gemtuzumab ozogamicin and clofarabine along with newer chemotherapeutics as mentioned in **Table 3** have shown some activity in clinical trials.

MORE ON THIS TOPIC

Gamis AS, Alonzo TA, Gerbing RB, et al. Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. Blood. 2011;118:6752-9.

Gibson BE, Wheatley K, Hann IM, et al. Treatment strategy and long-term results in pediatric patients treated in consecutive UK AML trials. Leukemia. 2005;19:2130-8.

Gilliland DG, Jordan CT, Felix CA. The molecular basis of leukemia. Hematology Am Soc Hematol Educ Program. 2004. pp. 80-97.

Kaspers GJ, Creutzig U. Pediatric acute myeloid leukemia: international progress and future directions. Leukemia. 2005;19:2025-9.

Maloney KW, Taub JW, Ravindranath Y, et al. Down syndrome: preleukemia and leukemia. Pediatr Clin North Am. 2015;62:121-37.

Mathews V, George B, Chendamarai E, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: long-term follow-up data. J Clin Oncol. 2010;28:3866-71.

Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011;29:551-65.

Ravindranath Y, Chang M, Steuber CP, et al. Pediatric Oncology Group (POG) studies of acute myeloid leukemia (AML): a review of four consecutive childhood AML trials conducted between 1981 and 2000. Leukemia. 2005;19:2101-16.

Ravindranath Y, Gregory J, Feusner J. Treatment of acute promyelocytic leukemia in children: arsenic or ATRA. Leukemia. 2004;18:1576-7.

Smith FO, Alonzo TA, Gerbing RB, et al. Long-term results of children with acute myeloid leukemia: a report of three consecutive Phase III trials by the Children's Cancer Group: CCG 251, CCG 213 and CCG 2891. Leukemia. 2005;19:2054-62.

IN A NUTSHELL

1. Majority of children develop de novo AML with no identifiable risk factor. Therapy-related AML from alkylating agents occurs 5–10 years after the exposure while AML after exposure to topoisomerase II inhibitors has a shorter latency period of 1–3 years.
2. Children with DS have a 600-fold greater chance of developing AML, particularly AML-M7. Children with DS are also known to have a form of spontaneously resolving leukemia, which is referred to as TMD or transient leukemia.
3. The diagnosis and characterization of AML requires morphology with cytochemistry, immunophenotyping by flow cytometry, cytogenetics and molecular genetics.
4. Despite new WHO classification, FAB classification remains useful clinically. It is important to differentiate M3 and M3v from other subtypes.
5. Cytogenetics represents the most important prognostic factor in newly diagnosed AML. The CBF leukemias, i.e., AML with t(8;21) and inv(16) are favorable risk AML and have significantly better OS.
6. Treatment of AML has been largely divided into induction chemotherapy and postremission (or consolidation) therapy. Supportive care and management of infections are of utmost importance.
7. The standard induction therapy consists of a combination of cytarabine and an anthracycline in a 7 + 3 strategy and remains as effective as any other induction regimen.
8. Consolidation therapy is risk based but usually consists of two to three cycles of high-dose cytarabine. Maintenance treatment showed no benefit. CNS prophylaxis is recommended for all children.
9. Auto-SCT is not recommended for children with AML while allo-SCT is reserved for intermediate- or high-risk patients.
10. Unlike other AML subtypes, in APML, CR can be achieved without the use of cytotoxic chemotherapy. ATRA and ATO alone or in combination is the therapy of choice.

Chapter 45.4
Chronic Myelogenous Leukemia
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Chronic myelogenous leukemia (CML) is a chronic hematopoietic stem cell disorder characterized by myeloid hyperplasia of bone marrow with extramedullary hematopoiesis, elevation of the total leukocyte count and a hallmark cytogenetic marker, the Philadelphia chromosome (Ph[1]), formed as a result of reciprocal translocation between chromosomes 9 and 22, which leads to a formation of a chimeric *BCR-ABL* fusion gene. Since the pediatrician acts as a vital link between the patient and oncologist, an insight into the CML disease dynamics is quite essential for an early diagnosis and shared care. An appropriately planned diagnostic evaluation aids in planning of an optimal therapy and follow-up.

EPIDEMIOLOGY

Chronic myeloid leukemia constitutes 3% of all newly diagnosed pediatric leukemias. The annual incidence of CML is around 1–2 cases per 75,000–100,000 population with a slight male preponderance in the West. This is most commonly diagnosed in the older adolescents in the pediatric age range. From Indian registries, the incidence of CML in the pediatric age group of 0–14 years is reportedly 0.11/100,000 for males and 0.09/100,000 for females; and 0.40/100,000 males and 0.23/100,000 females in the age group of 15–29. With the tyrosine kinase inhibitor (TKI) revolutionizing the treatment of CML, the prevalence of the disease is steadily increasing over time. There are no known factors implicated in the genesis of CML except for exposure to ionizing radiation reported in a few cases.

CYTOGENETICS IN CML

The cytogenetic hallmark of CML is Ph[1]. Only 5–10% of children with otherwise typical CML do not manifest Ph[1] chromosome; in some of these, Ph[1] chromosome may be masked by translocation of additional genetic material to 22q11 region. The Ph[1] chromosome is formed in a reciprocal balanced translocation between the long arms of chromosomes 9 and 22. The result of a Ph[1] translocation is the formation of chimeric fusion gene, *BCR-ABL* with a dysregulated tyrosine kinase activity. Apart from CML, the Ph[1] is also found in 3% of children with acute lymphoblastic leukemias. The clinical phenotype of the *BCR-ABL* encoding the tyrosine kinase as 210 kDa (p210) is CML and as 190 kDa (p190) is the B-cell lineage acute lymphoblastic leukemia. A majority of the CML children develop additional clonal aberrations in the advanced phases of the disease indicating a genomic instability. This hallmark cytogenetics of CML is tapped in the diagnostics and follow-up as discussed subsequently. The conventional karyotyping in CML is by G banding and *BCR-ABL* fusion by fluorescence in situ hybridization (FISH).

PATHOGENESIS

The evolution of CML from chronic phase to accelerated phase to blast crisis involves a multistep pathogenesis. The development of chronic phase of CML is the direct result of *BCR-ABL* activity triggering a hyperproliferation of cells. The multistep process is as depicted in **Flow chart 1**.

CLINICAL FEATURES

The natural history of chronic myeloid leukemia is characterized by three phases: (1) chronic phase, (2) accelerated phase and (3) the blast phase representing the progression of disease from hyperproliferation of mature cells to differentiation arrest with increase in immature cells. The clinical features, lab findings and cytogenetics in each phase are summarized in **Table 1**. Approximately 95% of the children will present in chronic phase

Flow chart 1 Pathogenesis of chronic myeloid leukemia
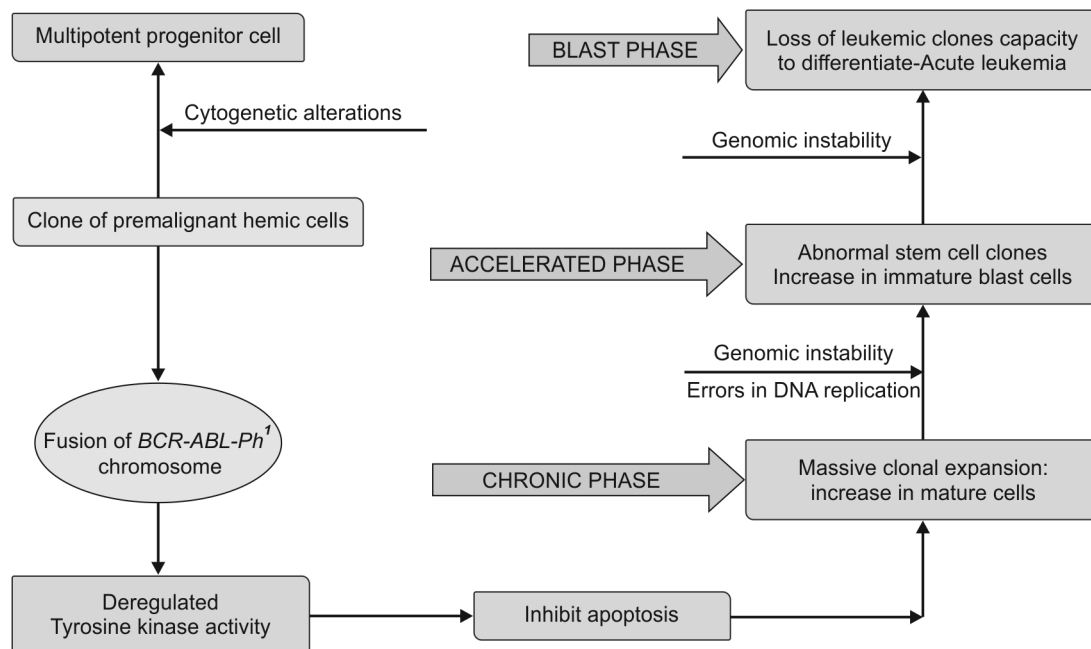
Table 1 Typical clinical and laboratory findings and cytogenetics in each phase of chronic myelogenous leukemia (CML)

	Chronic phase	Accelerated phase	Blast crisis
Clinical features	Fever, night sweats, weakness, left upper quadrant pain, bone pain, pallor and hepatosplenomegaly	Fever, night sweats, weight loss	Fever, weight loss, pallor, easy bruisability, pruritus and urticaria (due to basophilia)
Laboratory findings	• Anemia—normocytic normochromic • *Leukocytosis:* 8,000–800,000/mm^3, shift to left • Thrombocytosis • *Peripheral smear:* Myeloid cells at all stages of differentiation, myeloblasts < 15%, increase in basophils and eosinophilia • *Uric acid:* May be elevated • *LDH:* Elevated • *Bone marrow:* Hypercellular with granulocyte hyperplasia, eosinophilia, basophilia and increased megakaryocytes, blasts < 10%	• Anemia—normocytic normochromic • Leukocytosis—marked, shift to left • Thrombocytosis/thrombocytopenia • *Peripheral smear:* High proportion of immature cells, basophilia, blasts • *Uric acid:* Elevated • *LDH:* Elevated • *Bone marrow:* Hypercellular, basophilia, increase in blasts	• Anemia • Leukocytosis—marked • Thrombocytopenia • *Peripheral smear:* High proportion of immature cells with increased blasts • *Uric acid:* Elevated • *LDH:* Elevated • *Bone marrow:* Hypercellular, basophilia with myeloblasts (rarely lymphoblasts)
Cytogenetics	t(9;22) fusion	• Duplication of Ph[1] chromosome • Isochromosome 17 • Trisomy 8 • Trisomy 19	Clonal evolution

Table 2 Diagnostic criteria of chronic, accelerated and blast phases of chronic myelogenous leukemia (CML)

CML-CP	**Must meet all of the following criteria:** • Documentation of t(9;22) or the *BCR-ABL* fusion gene • Bone marrow blasts < 10% • Does not meet any criteria for accelerated phase or blast crisis
CML-AP	**Must meet one or more of the following criteria:** • Blasts 10–19% of peripheral WBCs or bone marrow cells • Peripheral blood basophils at least 20% • Persistent thrombocytopenia (100 × 10^9/L) unrelated to therapy or persistent thrombocytosis (100 × 10^9/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy • Cytogenetic evidence of clonal evolution • Megakaryocytic proliferation in sizable sheets and clusters, with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia
CML-BC	**Must meet one or more of the following criteria:** • Blasts ≥ 20% of peripheral WBCs or bone marrow cells • Extramedullary blast proliferation • Large clusters or foci of blasts in bone marrow biopsy

of the disease. The criteria for the chronic, accelerated and blast phases as per the WHO classification are as described in **Table 2**.

COMPLICATIONS

Children with CML can present with complications due to metabolic consequences or leukostatic complications owing to the high leukocyte count.

Metabolic disorders Rapid cell turnover may lead to metabolic derangements like hyperuricemia, hyperkalemia and hyperphosphatemia in children with CML which needs to be anticipated and managed appropriately.

Hyperleukocytosis The leukostatic complications due to high leukocyte count are especially seen in brain, lung, retina and penis. Children with myeloblastic transformation are at high-risk for this. Hence children with symptomatic hyperleukocytosis might require immediate treatment with drugs or leukapheresis.

Thrombocytosis This may be associated with thromboembolic or hemorrhagic complications.

Priapism This results from either mechanical obstruction by leukemic cells, coagulation within corpora cavernosa secondary to thrombocytosis or impingement by the spleen on abdominal veins and nerves.

Meningeal leukemia This is a rare complication seen in blast transformation and may present with cranial nerve palsies and papilledema.

DIFFERENTIAL DIAGNOSIS

Chronic phase CML Since a majority of children with CML present in the chronic phase, it is very important to distinguish them from leukemoid reactions and other myeloproliferative disorders like juvenile myelomonocytic leukemia (JMML). The demonstration of Ph[1] chromosome is the final differentiating factor. **Table 3** briefly enumerates the differences between the three (leukemoid reactions, JMML and CML).

Blast crisis Blast crisis in a child with documented chronic phase of CML does not cause any difficulty in diagnosis but it is those rare cases who present with blast crisis without a documented preceding chronic phase pose a dilemma for diagnosis. A child with Ph[1]-positive acute lymphoblastic leukemia needs to be differentiated from a child with CML in blast crisis. The presence of marked splenomegaly, basophilia, Ph[1] chromosome with *BCR* rearrangements at p210 and the typical clonal karyotypic evolutions in the blast phase of CML will establish the diagnosis.

APPROACH TO DIAGNOSIS

A high index of suspicion is required when a child presents with fever, night sweats, weakness, left upper quadrant pain, bone pain, pallor and hepatosplenomegaly, without an obvious inflammatory focus. A diagnostic work-up for CML includes complete blood counts and peripheral smear. The smear shows myeloid cells at all stages of differentiation, basophilia, eosinophilia and a few blast cells **(Fig. 1)**. A typical bone marrow aspirate shows hypercellular marrow with granulocyte hyperplasia **(Fig. 2)**. Demonstration of t(9;22) translocation on a marrow aspirate cytogenetics by G-banding and FISH **(Figs 3A and B)** clinches the diagnosis. Biochemical investigations are done for detection of tumor lysis—serum uric acid, lactate dehydrogenase (LDH), serum potassium, serum creatinine, serum calcium, and serum phosphorus. Specialized investigations include a FISH and quantitative polymerase chain reaction (PCR) for *BCR-ABL* in the peripheral blood.

Table 3 Differential diagnosis of chronic phase of chronic myelogenous leukemia

	Leukemoid reactions	*Juvenile myelomonocytic leukemia (JMML)*	*Chronic myelogenous leukemia (CML)*
Splenomegaly	Not marked	Less marked	Marked
Peripheral smear	Mature neutrophilic leukocytosis, marked shift to left, toxic granules	Monocytosis	Increased myeloid cells with eosinophilia and basophilia
Leukocyte alkaline phosphatase (LAP) score	High	Low	Low
Cytogenetics analysis	No cytogenetic abnormalities	Ph[1]-negative	Ph[1]-positive
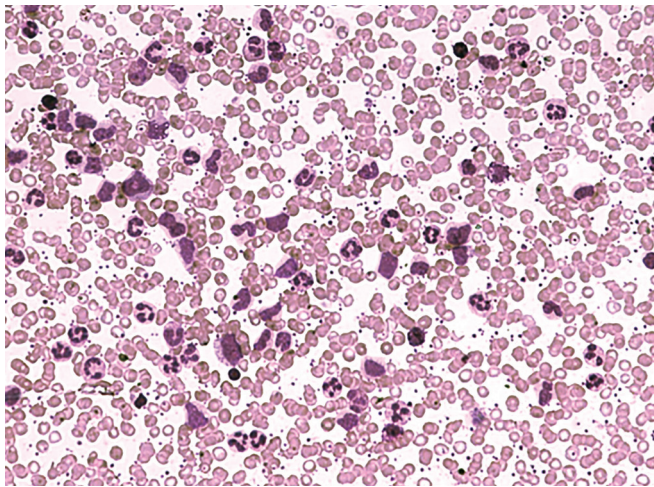
Figure 1 Peripheral smear in a chronic myeloid leukemia showing myeloid cells at all stages of differentiation, basophilia and eosinophilia
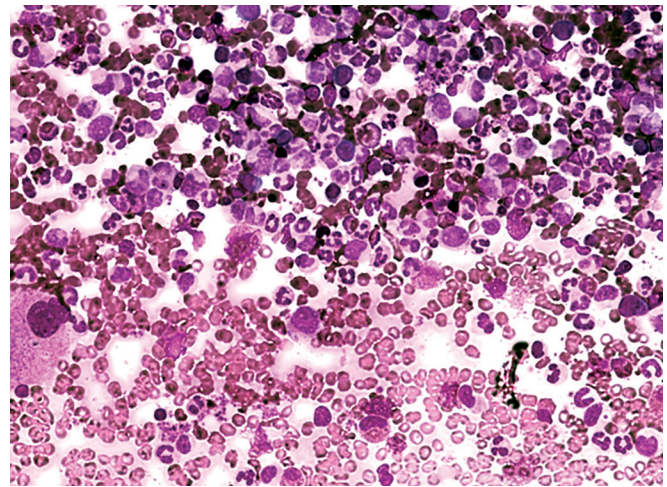
Figure 2 Bone marrow aspirate (Leishman stain) in chronic myeloid leukemia showing hypercellular marrow with granulocyte hyperplasia
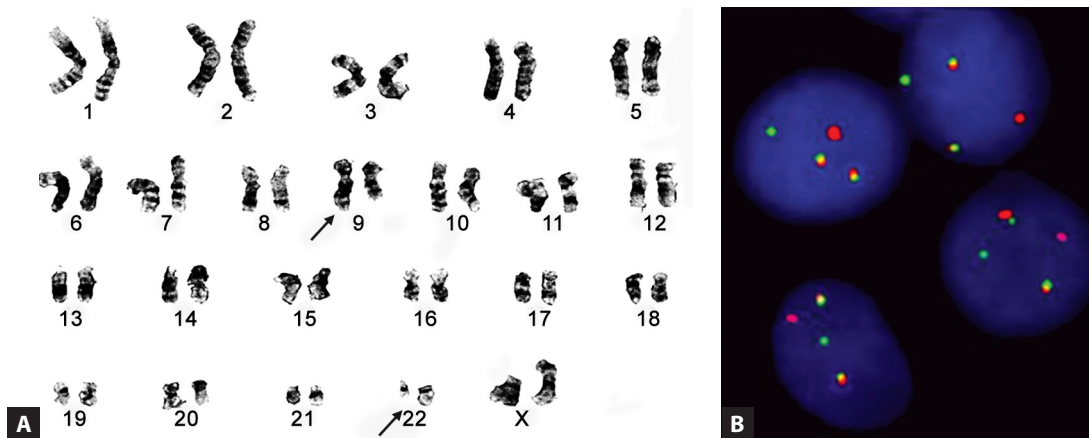
Figures 3A and B (A) Bone marrow karyotyping showing translocation 9;22 by G banding and (B) FISH showing *BCR-ABL* fusion

MANAGEMENT

Chronic Phase CML

The initial priority in this phase of CML is to achieve a cytoreduction. This is achieved by hydroxyurea, TKIs and interferon-α. Hydroxyurea is a ribonucleoside diphosphate reductase inhibitor and started at 25–50 mg/m²/day and adjusted as per hematologic response. The therapy of CML has been revolutionized by introduction of TKIs.

Imatinib mesylate This molecule is a first-generation TKI which blocks the activity of BCR-ABL protein thereby leading to apoptosis. The recommended starting dose is 340 mg/m² once

daily (available as 100 mg and 400 mg tablets). This is metabolized in the liver and liquid formulations may also be prepared. Tablets may be dispersed in water or apple juice using 50 mL for 100 mg and 200 mL for 400 mg tablet. It is generally well tolerated. Side effects include hematologic toxicity: anemia, neutropenia or thrombocytopenia; rash, elevated liver functions, muscle cramps, nausea, vomiting, headache, edema, cardiac toxicity: prolongation of QT interval, effusions, growth retardation, hypocalcemia, and hypophosphatemia.

Monitoring of response to TKI After a child is started on imatinib, laboratory monitoring of disease burden is recommended for measuring response to imatinib therapy. This includes hematologic

response, cytogenetic response and molecular response. The different levels of response are defined as shown in **Flow chart 2**. Complete blood counts are done once a month. Bone marrow with cytogenetics/FISH is done every 3 months until complete cytogenetic response (CCyR), and then every 6 months. Peripheral blood quantitative PCR for *BCR-ABL* is done every 3 months until major molecular response (MMR), and then every 6 months. The expected response at various therapeutic time points is depicted in **Figure 4**. TKI mutation analysis needs to be done whenever there is any measure of suboptimal response on TKI.

Second-generation TKI Dasatinib and nilotinib have recently emerged in the treatment of CML. Dasatinib binds to both active and inactive conformation of the *ABL* kinase domain. A dose of 80 mg/m^2 is well tolerated. Nilotinib is highly selective with a potency of 10–50 times that of imatinib. T315I mutation results in a phenotype which is resistant to imatinib, dasatinib, nilotinib and many of the newer *ABL* kinases but is responsive to third-generation TKI called ponatinib.

Interferon-α is used in patients intolerant to TKI.

Stem cell transplantation Allogeneic stem cell transplantation though appears to be a proven curative therapy for children with CML but is achieved at the cost of transplant-related mortality in comparison to imatinib which is relatively nontoxic and has high rates of remission. TKIs reduce the disease burden at the time of transplantation and hence these patients seem to have a lower risk of death as compared to those who did not receive imatinib before transplant. If a patient has suboptimal response or fails therapy after switching over to second-generation TKI, screening for a matched donor and proceeding to stem cell transplant needs to be considered.

Time point	Hematological response (HR)			Cytogenetic response (CyR)				Molecular response (MR)	
	None or less than partial	Partial HR	Complete HR	None	Minor or minimal CyR	Partial CyR	Complete CyR	<Major MR	Major MR
3 months	Failure	Suboptimal	Optimal	Suboptimal	Optimal	Optimal	Optimal	Optimal	Optimal
6 months	Failure	Failure	Failure	Failure	Suboptimal	Optimal	Optimal	Optimal	Optimal
12 months	Failure	Failure	Failure	Failure	Failure	Suboptimal	Optimal	Optimal	Optimal
18 months	Failure	Failure	Failure	Failure	Failure	Failure	Suboptimal	Suboptimal	Optimal

■ Failure
■ Suboptimal response
■ Optimal response

Figure 4 Response criteria to tyrosine kinase inhibitor (TKI)

Accelerated Phase

Start imatinib at 400 mg/m^2 or dasatinib at the dose of 80 mg/m^2/day in two divided doses and start hydroxyurea at 25–50 mg/m^2/day. Screen for human leukocyte antigen (HLA)-matched sibling donor or unrelated donor and proceed to transplant when in remission. **Box 1** shows key aspects in treatment of CML.

Blast Crisis

Start imatinib at 500 mg/m^2 or dasatinib at the dose of 80 mg/m^2/day in two divided doses. Start antileukemia chemotherapy. Treatment regimens are based on whether there is myeloblastic or lymphoblastic transformation with the latter group being more

Flow chart 2 Different levels of hematologic, cytogenetic and molecular responses to tyrosine kinase inhibitor (TKI)

Response to TKI

Hematologic response
This is assessed by performing peripheral complete blood counts

Cytogenetic response
This is assessed by bone marrow cytogenetic analysis and peripheral blood FISH analysis

Molecular response
This is measured by the quantitative PCR, a sensitive marker of detection of *BCR-ABL* and is able to detect 1 in 100,000 cells

• **Partial hematological response (PHR):**

• WBC > 10,000 cells/mm^3
• Platelets > 450,000/mm^3
• But > 50% reduction in blasts and
• Presence of immature cells with splenomegaly

• **Complete hematological response (CHR):**

• WBC < 10,000 /mm^3
• Platelets < 4,50,000 /mm^3
• Absence of immature cells and splenomegaly
• < 5% basophils

• **Minimal cytogenetic response:**

66–95% Ph$^+$ metaphases in marrow culture

• **Minor cytogenetic response:**

36–65% Ph$^+$ metaphases

• **Major cytogenetic response (MCyR)**

• Partial cytogenetic response (PCyR): 1–35% Ph$^+$ metaphases
• Complete cytogenetic response(CCyR): 0% Ph$^+$ metaphases

• **Major molecular response (MMR):**

> 3-log reduction in *BCR-ABL* transcripts from diagnosis or < 0.1%
• **Complete molecular response (CMR):**

No *BCR-ABL* transcripts detectable by quantitative PCR

sensitive to chemotherapy. Screen for HLA-matched sibling donor or unrelated donor and proceed to transplant when in remission.

Studies have reported significant responses to imatinib mesylate with acceptable toxicity in children with advanced stages of CML. Complete hematologic response (CHR) of 75% in advanced phase CML have been reported in children. Imatinib dose escalation applied as a strategy in children who do not show the expected response and in advanced phases has shown some benefit.

Management of Complications

Metabolic disorders need to be appropriately managed with hydration and allopurinol as per the guidelines for tumor lysis. Hyperleukocytosis should be treated by cytotoxic drugs—hydroxyurea and if needed, leukapheresis. Treatment of priapism includes analgesia, hydration, application of warm compresses, and initiation of chemotherapy.

OUTCOMES/PROGNOSTIC FACTORS

The duration of chronic phase as well as peripheral blood and bone marrow blast counts are considered to be of prognostic significance in children with a high proportion of blast cells, conferring a poor prognosis. With imatinib forming the cornerstone of therapy in pediatric CML, there is a debate on the long-term control of disease versus the cure achieved by stem cell transplant. The success of

TKI in children has been remarkable with recent trials in children showing 90–100% CHR, 70–90% major cytogenetic response, 70–90% CCyR, and 45–75% MMR at 36 months. In children with accelerated and blast phases, 75% CHR and 29% CCyR have been achieved. A progression-free survival of 98% at the end of 2 years has been achieved in children.

MORE ON THIS TOPIC

Altman AJ. Fu C. Chronic leukemias of childhood. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2011. pp. 610-29.

Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. Blood. 2012;119:1821-30.

Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122:872-84.

Lanzkowsky P. Chronic myeloproliferative diseases. In: Lanzkowsky P. Manual of Pediatric Hematology and Oncology. 5th ed. USA: Elsevier; 2011. pp. 508-15.

BOX 1 Key aspects in treatment of chronic myelogenous leukemia (CML)

- Tyrosine kinase inhibitor—*imatinib mesylate* is the cornerstone of treatment in the chronic phase of CML

- *Dose*: Started at 340 mg/m^2 and continued indefinitely in chronic phase and 400–500 mg/m^2 in advanced phase

- Monitoring of response to TKI is done by complete blood counts, bone marrow cytogenetics/FISH and quantitative PCR for *BCR-ABL*

- Hydroxyurea at 25–50 mg/m^2/day is initially added to achieve cytoreduction

- Tumor lysis and hyperleukocytosis need to be addressed appropriately

- Dasatinib, a second-generation TKI, at a dose of 80 mg/m^2 is used when there is suboptimal response on imatinib as well as in accelerated phase

- Stem cell transplantation is required for children who fail the first-line therapy with TKI or have advanced phase CML after cytoreduction with TKI

- Stem cell transplant is to be considered in suboptimal response and blast phase.

IN A NUTSHELL

1. Chronic myelogenous leukemia is a chronic hematopoietic stem cell disorder characterized by myeloid hyperplasia of bone marrow.

2. The hallmark cytogenetic marker of CML is the Philadelphia chromosome (Ph[1]) [t (9,22)] resulting in *BCR-ABL* fusion gene.

3. Chronic myelogenous leukemia is characterized by three phases: (1) chronic phase, (2) accelerated phase and (3) blast phase.

4. The typical diagnostic findings of a peripheral smear in chronic phase consist of myeloid cells in all stages of maturation, few blasts with basophilia.

5. A child in chronic phase can present in tumor lysis, hyperleukocytosis, priapism or thrombocytosis.

6. Imatinib mesylate, a first-generation TKI is the first line of therapy in the chronic phase of CML. The response to TKI therapy is monitored by complete blood counts, bone marrow cytogenetics/FISH and peripheral blood quantitative PCR for BCR-ABL transcripts.

7. Dasatinib, a second-generation TKI is used in suboptimal responses and in advanced phases.

8. The long-term control of imatinib along with minimal acute and chronic morbidity has outweighed the benefits associated with stem cell transplantation in CML which being curative was considered the first-line option till recently.

Chapter 45.5

Myelodysplastic Syndrome and Juvenile Myelomonocytic Leukemia

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MYELODYSPLASTIC SYNDROME

Childhood myelodysplastic syndrome (MDS) is a group of bone marrow disorders with defective stem cell maturation, impaired hematopoiesis and dysplastic changes in the marrow resulting into cytopenias which may be absolute and/or functional. The bone marrow has less than 20% blasts and may have normal, hypo- or hypercellularity.

Myelodysplastic syndrome disorders have a tendency to transform into leukemias mostly myeloid leukemias, and hence are referred as preleukemias. Until recently, the childhood MDS was poorly defined, studied and reported. This lack of understanding was because of poor understanding of the biologic mechanisms of the disease, rarity of the disease, lack of uniform diagnostic criteria and use of adult criteria for classification and prognostic system.

EPIDEMIOLOGY

Myelodysplastic syndrome and juvenile myelomonocytic leukemia (JMML) constitute 6–8% of childhood leukemia. The reported annual incidence in studies from the United Kingdom, Denmark and British Columbia is 1.8–4 cases per million in pediatric and adolescent population (age group 0–14 years). Many studies have confirmed presence of preleukemia/MDS in about 12–20% of acute myeloid leukemia (AML) cases.

There is paucity of data on incidence of MDS from India. Two studies from AIIMS have reported 90 cases over a period of 16 years (1980–1995) and 21 cases over a period of 3 years (2001–2004), accounting for about 6% cases of hematological malignancies, similar to figures quoted from other centers. There is a dearth of epidemiologic literature on childhood MDS. The reasons for which may be due to lack of an acceptable classification, nonreferral of indolent cases to tertiary centers and the MDS cases not being registered in cancer registries.

ETIOLOGY

Multiple factors such as certain genetic disorders and environmental exposures have been noted to predispose patients to the development of MDS **(Table 1)**. Certain chromosomal anomalies, which are definitely linked with MDS like chromosome 5 deletion and monosomy 7 have been associated with past therapy with alkylating agents. Topoisomerase inhibitors are a contributing

Table 1 Childhood myelodysplastic syndrome (MDS)-associated conditions

Congenital	Acquired
• Congenital neutropenia • Congenital bone marrow disorders • Diamond-Blackfan anemia • Fanconi anemia • Shwachman-Diamond syndrome • Trisomy 21 • Trisomy 8 • Type 1 neurofibromatosis	• Immunosuppressive therapy in aplastic anemia • Previous exposure to chemotherapy or radiotherapy

factor in rare cases, and these patients usually have been reported to develop AML.

In 10–15% patients of acquired aplastic anemia, MDS may occur within 3 years of presentation. The frequency is same in hepatitis-associated and idiopathic aplastic anemia. The role of use of cyclosporine and granulocyte colony-stimulating factor (G-CSF) therapy in these patients as a cause of MDS is controversial.

PATHOGENESIS/PATHOPHYSIOLOGY

Many different pathophysiologic mechanisms have been implicated in initiation and progress of this heterogeneous disease. It is a clonal disorder arising from multi- or pluripotent stem cells. The current postulation is there is initial domination of apoptosis. This is followed by maturational arrest and proliferation, which results from progressive accumulation of more genetic abnormalities in MDS cells and leads to transformation into AML. Loss of genetic material from chromosomes, particularly so from long arms of chromosome 5 and 7 (5q and 7q), has been implicated in the pathogenesis of MDS. These regions are site for tumor suppressor genes and have a definite role in hematopoiesis.

CLASSIFICATION

A number of criteria for classifying MDS have been proposed **(Tables 2 and 3; Box 1)**. The classification systems are based on clinical examination, findings of peripheral smears, cytogenetics and bone marrow histology. Classification based on frequency, treatment difficulties and outcomes has been proposed but has many controversies. In adults, French-American-British (FAB) classification is the most accepted. Five distinct forms of MDS are recognized in this classification: (1) refractory anemia (RA), (2) refractory anemia with excess blasts (RAEB), (3) refractory anemia with excess blast in transformation (RAEB-T), (4) refractory anemia with ringed sideroblast (RARS) and (5) chronic myelomonocytic leukemia (CMML). But entities such as hypoplastic MDS, secondary MDS (related to therapy), MDS with myelofibrosis, MDS with inherited conditions (e.g., neurofibromatosis type 1, Shwachman syndrome) and cytopenias with trilineage dysplasias are not included in this

Table 2 Myelodysplastic syndrome (MDS) classification (Based on etiology)

Primary MDS	Secondary MDS
• Previously healthy child • No known predisposing condition	• Familial myelodysplastic syndrome • Therapy related (previous exposure to chemo- or radiotherapy) • Associated with inherited bone marrow failure syndromes

Table 3 Myelodysplastic syndrome (MDS) and myeloproliferative diseases (MPD) in children (WHO 2003 classification)

MDS/MPD	Myeloid proliferation in Down syndrome	MDS
• Juvenile myelomonocytic leukemia (JMML)	• Transient abnormal myelopoiesis (TAM) • Myeloid leukemia of Down syndrome (ML-DS)	• *Refractory cytopenias* (peripheral blasts < 2% and marrow blasts < 5%) • *Refractory anemia with excess blast* (peripheral blood blasts 2–19% or marrow blasts 5–19%) • *Refractory anemia with excess blast in transition* (peripheral blood or marrow blasts < 20–29%)

- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess of blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
- Refractory cytopenia of childhood (RCC)—provisional entity

MDS in children

- Refractory cytopenia of childhood
- Refractory anemia with excess of blasts (RAEB)
- Refractory anemia with excess of blasts in transformation (RAEB-T)

classification. Also prognostic implications of cytogenetics are not included in this classification.

Childhood MDS is different from adult MDS in many ways. CMML and RARS are extremely rare in pediatric patients. JMML and transient myeloproliferative disease (TMD) are only seen in pediatric population. Childhood MDS may be associated with constitutional abnormalities but this association is very rare in adults. Certain cytogenetics like 5q deletion is extremely rare in pediatric while monosomy 7 is common. The World Health Organization (WHO) 2003 classification is more appropriate for pediatrics, as it includes special entities like MDS associated with Down syndrome and JMML. WHO 2008 classification has included childhood MDS and cytopenias as special category **(Table 3; Box 1)**.

CLINICAL FEATURES

The children may be well looking or may have constitutional wasting. Other symptoms like pallor, infections, petechiae and bruises may be present related to cytopenias. Usually, there is no organomegaly and lymphadenopathy. Elevated hemoglobin F levels and macrocytosis are seen in children with RA, though there may not be low hemoglobin levels **(Box 2)**.

DIFFERENTIAL DIAGNOSIS

A detailed clinical history, systemic physical examination, examination of peripheral smear and evaluation of bone marrow for cytogenetic clonal abnormality and dysplastic examination can identify most cases of childhood MDS. Other conditions which should be considered in differential diagnosis are:

- Nutritional deficiencies such as vitamin B_{12} and folate deficiency as they present with megaloblastoid changes in marrow which appear similar to dysplastic changes

BOX 2 Clinical features of myelodysplastic syndrome (MDS) in children

- *Variable general appearance*: Constitutional wasting or completely well looking
- Symptoms and signs of marrow failure—infections, petechiae, pallor
- Presentation may mimic leukemia
- No liver and spleen enlargement in most patients (common in JMML)
- Lymphadenopathy seen in up to 10% cases (50–60% JMML)
- Erythematous maculopapular rash (30% JMML)

- Other nutritional deficiencies such as iron, riboflavin, pyridoxine and thiamine
- Viral infections—cytomegalovirus (CMV), human herpesvirus 6, human immunodeficiency virus, parvovirus
- Toxins—exposure to arsenic, chemotherapy, insecticides
- Paroxysmal nocturnal hemoglobinuria
- *Severe aplastic anemia*: To differentiate aplastic anemia from hypoplastic MDS is difficult. Repeated evaluations are necessary to reach a diagnosis. Bone marrow evaluations also may need to be repeated. Children who develop MDS after a diagnosis of aplastic anemia usually present within first 3 years of diagnosis
- Pearson syndrome should be considered, if RARS is suspected.

APPROACH TO DIAGNOSIS (BOXES 2 TO 4)

Diagnostic studies for suspected MDS should include a complete blood count (CBC) with differential, peripheral blood smears, bone marrow aspiration and biopsy. On the CBC, patients often have anemia with high red cell distribution width (RDW) and mean corpuscular volume (MCV). Other cell lines such as neutrophils and platelets may be reduced as well. Usually, high white blood cell (WBC) count is not a feature of MDS.

Other studies to rule out marrow suppression resulting from viral illnesses include CMV and Epstein-Barr virus (EBV) status.

BOX 3 Diagnostic criteria for myelodysplastic syndromes in children

At least two of the following:

- Persistent unexplained cytopenia (anemia, reduced neutrophils, low platelets)
- At least two cell line morphologic myelodysplasia
- Acquired clonal cytogenetic abnormality in hematopoietic cells
- Blasts ≥ 5%

BOX 4 Work-up of suspected myelodysplastic syndrome

History
- Family history
- Previous chemotherapy/radiotherapy

Examination
Clinical syndromes:
- Fanconi anemia
- Neurofibromatosis
- Noonan syndrome
- Shwachman-Diamond syndrome
- Trisomy 21

Laboratory tests
- CBC with differential to look for
  - Single lineage cytopenia
    - Hb < 10 g/dL in 50% patients
    - Severe neutropenia (seen in 25% cases)
    - Low platelets (seen in 75% cases)
  - Pancytopenia
  - High MCV
  - WBC counts: Low to normal
- Peripheral smear
- Fetal hemoglobin—moderately elevated hemoglobin F
- Virology—cytomegalovirus, Epstein-Barr virus and parvovirus
- Bone marrow aspiration and biopsy
- Morphology of marrow, especially of megakaryocytes, cellularity and fibrosis
- Cytogenetics with FISH
- Presence of abnormally localized immature precursor cells (ALIP)
- Studies for cytomegalovirus, Epstein-Barr virus
- Folate and B_{12} studies
- HLA typing

Deficiencies of folate and vitamin B_{12} need to be ruled out. Human leukocyte antigen (HLA) typing of the family and patient is done as hematopoietic stem cell rescue may be required in these patients.

Cytogenetics

Bone marrow cytogenetics including FISH should be done as part of investigations of patients with MDS. Approximately 90% of patients with secondary and 50% of primary MDS have cytogenetic abnormalities. Patients with MDS have partial deletions and chromosomal losses more common than translocations, a main distinctive property from AML. The most common cytogenetic abnormality in childhood MDS is monosomy 7, it does not have prognostic significance. The second most common abnormalities are trisomy 8 and 21.

TREATMENT RECOMMENDATIONS AND PROGNOSIS

Refractory anemia or refractory cytopenia It is recommended that children with RA be observed and closely monitored, because they usually have a long and indolent course. The median time to convert to RAEB is 47 months. Once they become transfusion dependent and susceptible to infections due to neutropenia, match-related stem cell transplant should be done. In absence of availability of related matched donor, alternate donor transplant may be considered.

Refractory anemia with excess blasts These patients usually have a high relapse rate, if cytoreduction is not done before hematopoietic stem cell transplantation (HSCT). Hence, before HSCT, it is recommended to give AML like chemotherapy. But this approach is still controversial. Also for those who are not in remission after AML chemotherapy, it is controversial whether to give more chemotherapy or perform HSCT. If a suitable matched related donor is not available, then an alternate donor should be considered.

Refractory anemia with excess blasts in transformation These patients are treated with AML like chemotherapy followed by HSCT preferably from matched related donor. An alternated donor is considered, if matched related donor is not available.

The only curative treatment for MDS is allogeneic HSCT. Other therapies are not effective.

OUTCOME/PROGNOSTIC FACTORS

The International Prognostic Scoring System (IPSS) studies were done in adults but its use in pediatric patients is limited. The scoring system is summarized in **Table 4**. For pediatric patients, FPC (hemoglobin **F**, **p**latelet, **c**ytogenetics) has been found more useful and given in **Table 5**.

Table 5 FPC scoring system for prognostic classification of childhood MDS

Criteria (before start of treatment)	Points
Fetal hemoglobin > 10%	1
Platelet ≤ 40,000/mm³	1
Cytogenetics	
• No clonal abnormalities	0
• Simple abnormalities (resulting from single translocation, loss or gain of one chromosome, other structural abnormalities)	1
• Complex abnormalities (resulting from two or more numerical or structural events)	2
Score	5-year survival (%)
0	61
1	20
2 or 3	0

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia, a rare hematopoietic malignancy of childhood, accounts for about 2% of all childhood leukemias. The WHO reclassified, it by removing JMML from MDS and placing it in the new category of myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). In the FAB classification, it falls in the MDS category.

EPIDEMIOLOGY

Juvenile myelomonocytic leukemia presents in younger children (median age 1 year) and is more common in boys (M:F 2.5:1). Predisposing conditions include neurofibromatosis type 1 (14% of cases) and Noonan syndrome carrying the germline *PTPN11* mutations. *PTPN11* mutations, germline and somatic, account for 35% of all JMML cases.

PATHOGENESIS

Juvenile myelomonocytic leukemia arises from a pluripotent stem cell. JMML mononuclear cells of blood or bone marrow when cultured in semisolid media without addition of growth factors exhibit spontaneous proliferation giving rise to an excessive number of monocyte-macrophage colonies. This is linked to the production of interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), or tumor necrosis factor (TNF) by the JMML mononuclear cells. This hypersensitivity to endogenous GM-CSF is a hallmark and a diagnostic tool for the

Table 4 International Prognostic Scoring System, risk groups and 5-year survival for myelodysplastic syndromes

Variables→ Scores↓	Blasts in bone marrow (%)	Cytogenetics	Cytopenias	Risk group	5-year survival (%)
0	< 5	Good {Del (5q) Del (20q)-Y}	Single cell line or none	Low	100
0.5	5–10	Intermediate (All other abnormalities)	More than 1 lineages	Intermediate 1	72
1.0	5–10	Poor {Chromosome 7 abnormalities, Complex (> 3 abnormalities)}	–	Intermediate 1	72
1.5–2.0	11–20	–	–	Intermediate 2	40
2–2.5	21–30	–	–	High	40

condition. In studies conducted to understand the receptor and cytoplasmic signaling transduction and to uncover a defect in the GM-CSF signal transduction pathway, no GM-CSF receptor mutations were noted but there were pointers at abnormalities in the Ras/mitogen-activated protein kinase (MAPK) pathway. The fact that mutations in neurofibromatosis type 1, PTPN11, and Ras are mutually exclusive, suggests that activation of the Ras/MAPK cascade may be the reason for the hyperproliferation characteristics of JMML.

CLINICAL FEATURES AND DIAGNOSIS

The common presenting features of JMML are following: Constitutional symptoms (fever, pallor, malaise) or evidence of infection; hepatosplenomegaly (most cases) **(Fig. 1)**; lymphadenopathy (75% of cases); maculopapular skin rashes (40–50% of cases); bleeding diathesis.

On morphology, the peripheral blood picture reveals leukocytosis, thrombocytopenia and anemia. The WBC count is usually from 25×10^9/L to 35×10^9/L; however, it could be greater than 100×10^9/L. Leukocytosis comprises of monocytes and neutrophils with promyelocytes, myelocytes. Blasts, including promonocytes, are less than 5% of the WBCs. Nucleated red blood may be present. Thrombocytopenia is always present and may be severe **(Fig. 2)**.

Bone marrow findings include hypercellularity with granulocytic proliferation, decreased megakaryocytes, minimal dysplasia, monocytes 5–10% of marrow cells (30% in some). Laboratory testing as described earlier, exhibits spontaneous proliferation of the JMML mononuclear cells in vitro without the addition of exogenous stimuli. Philadelphia chromosome or BCR/ABL fusion gene are negative. Monosomy 7 is seen in 30–40% of patients, but is not specific for JMML. The clinical and laboratory features of JMML can closely mimic a variety of infectious diseases which need to be ruled out.

Differential diagnosis includes infections with EBV, human herpesvirus 6, *Histoplasma*, *Toxoplasma*, CMV, and mycobacteria. In children presenting with features suggestive of JMML, the diagnosis requires fulfillment of modified WHO criteria **(Table 6)**.

TREATMENT

There is no proven consistently effective therapy for JMML. Some young children with JMML may be in remission for long periods without therapy. Stem cell transplantation (SCT) is the only curative treatment modality achieving cure in 30–50% of patients. Role of antileukemic therapy before SCT is unknown.

6-mercaptopurine has been used with clinical and hematologic responses, but has no influence on the length of survival. Intensive therapy is complicated by treatment related morbidity and mortality; moreover, true remissions are not achieved. It is therefore, no longer advocated. Treatment with retinoic acid has been associated with remissions in a small number of patients. Molecular-targeting therapies currently being studied include farnesyltransferase inhibitors that prevent Ras protein maturation, which may result in tumor cell apoptosis and inhibit tumor cell growth.

PROGNOSIS

The course can be variable; survival varies from 10 months to more than 4 years, depending partly on the treatment. If left untreated, it is rapidly fatal in most children. Low platelet count, age more than 2 years, and raised hemoglobin F at diagnosis are the main prognostic factors for short survival. Prognosis is better in infants. Some cases may evolve into acute leukemia.

Patients follow one of three clinical courses: (1) have a rapidly progressive disease with early death, (2) stable disease for a

Table 6 Diagnostic criteria for juvenile myelomonocytic leukemia (JMML)

Category 1 (All of the following)*	Category 2 (at least one of the following)†	Category 3 (two of the following, if no category 2 criteria are met)*
Absence of the *BCR/ABL* fusion gene	Somatic mutation in RAS or PTPN 11	White blood cell count > 10,000 (10×10^9/μL)
> 1000 (1×10^9/μL) circulating monocytes	Clinical diagnosis of *NF1* or *NF 1* gene mutation	Circulating myeloid precursors Increased HbF for age
< 20% blasts in the bone marrow Splenomegaly†	Monosomy 7	Clonal cytogenetic abnormality excluding monosomy 7† GM-CSF hypersensitivity[3]

* Current WHO criteria
† Proposed additions to the WHO criteria discussed by participants attending the JMML Symposium in Atlanta, GA, 2008.

Figure 1 Child with juvenile myelomonocytic leukemia (JMML) with hepatosplenomegaly exhibiting abdominal fullness
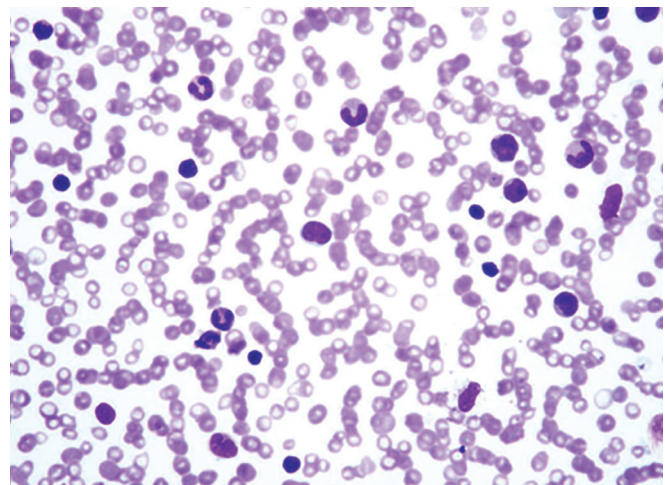
Figure 2 Juvenile myelomonocytic leukemia (JMML) blood smear showing leukocytosis with immature forms and monocytosis

variable time followed by progression and death, or (3) apparent remission that can last for as long as a decade before progression or, rarely, long-term survival.

MORE ON THIS TOPIC

Aricò M, Biondi A, Pui CH. Juvenile myelomonocytic leukemia. Blood. 1997;90:479-88.

Elghetany MT. Myelodysplastic syndromes in children: a critical review of issues in the diagnosis and classification of 887 cases from 13 published series. Arch Pathol Lab Med. 2007;131:1110-6.

Hasle H, Niemeyer CM, Chessells JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia. 2003;17:277-82.

Luna-Fineman S, Shannon KM, Atwater SK, et al. Myelodysplastic and myeloproliferative disorders of childhood: a study of 167 patients. Blood. 1999;93:459-66.

Loh ML. Childhood myelodysplastic syndrome: focus on the approach to diagnosis and treatment of juvenile myelomonocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:357-62.

Niemeyer CM, Arico M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a retrospective analysis of 110 cases. European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS). Blood. 1997;89:3534-43.

Niemeyer CM, Baumann I. Classification of childhood aplastic anemia and myelodysplastic syndrome. Hematology Am Soc Hematol Educ Program. 2011;2011:84-9.

Passmore SJ, Hann CA, Stiller CA, et al. Pediatric myelodysplasia: a study of 68 children and a new prognostic scoring system. Blood. 1995;85:1742-50.

Shende A, Lanzkowsky P. Myeloproliferative and myelodysplastic disorders. In: Lanzkowsky P. Manual of Pediatric Hematology and Oncology. 4th ed. London: Elsevier Academic Press; 2005. pp. 388-98.

Smith FO, Woods WG. Myeloproliferative and myelodysplastic disorders. In; Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. pp. 673-94.

Singh ZN, Kashyap R, Pati HP, Choudhry VP. Myelodysplastic syndromes in childhood and adolescence: clinical and hematological profile. Indian Pediatr. 2001;38:72-6.

IN A NUTSHELL

1. Childhood MDS is rare but has more aggressive clinical course than adults.
2. It is characterized by progressive cytopenias associate with dysplastic changes in the marrow.
3. About one half of the children with reported cases of MDS have clonal abnormalities involving chromosome 7 (usually monosomy 7).
4. The transition time of childhood MDS to acute leukemia is 14–26 months which is relatively short. Hence, shortly after the diagnosis, aggressive therapy like transplantation should be considered.
5. The long-term survival in MDS patients after conventional chemotherapy is 20–25%. The survival rates after bone marrow transplantation (BMT) is about 50%.
6. Children with trisomy 21 and MDS/AML have a long-term survival rates of more than 80%, as they are very responsive to conventional chemotherapy.
7. Juvenile myelomonocytic leukemia is a rare fatal hematopoietic disorder seen in the younger child.
8. It is a MDS/MPN disorder whose diagnostic criteria were laid down by Neimeyer et al. in 1998 and incorporated in the WHO classification 2008.
9. Presentation is at a young age with hepatosplenomegaly, monocytosis, anemia, thrombocytopenia, elevated hemoglobin F.
10. Viral infections can mimic JMML in clinical and laboratory findings; serological and cytogenetic analyses are required to discriminate between the two conditions.
11. Hypersensitivity to endogenous GM-CSF is the hallmark of JMML leukemia cells and an important diagnostic tool.
12. Low platelet count, age older than 2 years, and high hemoglobin F at diagnosis are poor prognostic factors.
13. Stem cell transplantation is the only curative treatment capable of cure in approximately 30–50% of patients.

Chapter 45.6
Hodgkin Lymphoma
Vishal Sondhi, Brijesh Arora

Lymphomas are the third most common group of cancers in children and adolescents in West, accounting for 10–15% of all newly diagnosed cancers in this age group. In India, lymphomas are the second most common malignancy in children ahead of central nervous system (CNS) tumors, especially in males. Lymphomas are broadly classified into two groups: (1) Hodgkin and (2) non-Hodgkin lymphoma (**Table 1**).

Hodgkin lymphoma (HL, formerly known as Hodgkin disease) was named after Thomas Hodgkin, who first described the disease and its associated abnormalities in the lymph system in 1832. HL, since then, has been classified as a lymphoreticular malignancy characterized by the orderly spread of disease from one lymph node group to another (contiguous spread). The biology and natural history of pediatric HL commensurates with that of its adult counterpart and with the use of risk-adapted therapy, greater than 90% long-term survival has been attained for children with HL. Hence, management designed to achieve maximal cure rates with fewest late effects of therapy is the current paradigm for children with HL.

EPIDEMIOLOGY

The incidence of HL is bimodal with regards to age. In developed countries, the early peak occurs in young adults (20–34 years), followed by a late peak in elderly (55–74 years). In contrast in developing countries, there is a trimodal distribution with the first peak occurring before adolescence followed by two regular peaks. Nearly 20–30% of all pediatric HL cases in developing countries occur before 5 years of age against ~5% in industrialized nations.

In India, unlike West, lymphomas are the second most common malignancies in children ahead of CNS tumors especially in males. Importantly, HL exceeds non-Hodgkin lymphoma in India in contrast to Western countries. The age standardized incidence of HL in Indian children ranges from 8.2/million children/year to 19.6/million children/year compared to 5.7 in the United States of America and 6.4 in Britain. Furthermore, mixed cellularity is most common phenotype in India leading to much younger age peak (median age 8–9 years) compared to 16–30 years in West where nodular sclerosis is most common. Pediatric HL shows a male predominance in low-income countries including India with a male:female ratio of 4:1 for children 3–7 years of age, 3:1 for children 7–9 years, and 1.3:1 for children greater than 10 years.

RISK FACTORS

The etiology of HL is believed to be multifactorial and may include the following:

Infectious agents Epstein-Barr virus (EBV) has been associated with HL by epidemiologic and serologic studies. EBV-DNA can be identified in Hodgkin Reed-Sternberg (RS) cells in nearly 50% patients in West and in more than 90% patients in developing countries. The cytogenetic techniques have shown the infection to be monoclonal; indicating that the virus infected population arose from a single infected cell. Also, EBV is most commonly associated with mixed cellularity and lymphocyte-depleted HL subtypes and less frequently with nodular sclerosis HL. With regard to age, EBV is commoner in children less than 10 years compared with adolescents and adults. Patients with a prior history of infectious mononucleosis have been shown to have a fourfold increased risk of developing EBV-positive HL. Other infectious agents such as human herpesvirus 6 (HHV 6), cytomegalovirus (CMV) have also been implicated but the linkage has been weak and inconclusive.

Genetic influences Clustering of cases in families or races suggests a genetic predisposition or exposure to a common infectious agent. The risk is postulated to be 100-fold for sibling of an affected monozygotic twin. In addition, familial HL is associated with specific human leukocyte antigens and represents 4.5% of all cases.

Immune dysregulation Immunodeficiency disorders, either congenital (like ataxia-telangiectasia) or acquired (like HIV infection) are associated with a higher risk of HL.

BIOLOGY

Hodgkin lymphoma is a B-lineage lymphoma defined histopathologically by the presence of clonal RS cells. RS cell is the malignant cell in HL, which is characteristically binucleate or multinucleate giant cell with prominent nucleoli and abundant cytoplasm. In certain subtypes of HL, the malignant cells are lymphocytic and histiocytic (L&H cells). RS cells usually constitute less than 1% of cells in involved lymph nodes. The rest of lymph node contains a variable cellular infiltrate consisting of lymphocytes, eosinophils, macrophages, plasma cells, and fibroblasts. These infiltrating cells secrete an array of cytokines and chemokines that are important for RS cells survival and maintenance of characteristic cellular infiltrate. These malignant cells have three distinct origins (**Table 2**).

Table 1 Comparative clinical features of Hodgkin and non-Hodgkin lymphoma

Clinical features	Hodgkin lymphoma	Non-Hodgkin lymphoma
Nodal spread	Contiguous	Discontiguous
Localized	Yes	Rare
Extranodal disease	Rare	Common
CNS disease	Rare	Common
Bone marrow involvement	Rare	Common
B symptoms	Common	Uncommon
Abdominal disease	Uncommon	Common
Subtype based therapy	Not important	Crucial
Cure rates	85–95%	70–80%

Table 2 Immunophenotypes of malignant cells in Hodgkin lymphoma

	Nodular lymphocyte-predominant Hodgkin lymphoma	Classical Hodgkin lymphoma
Antigen		
J chain	+	−
CD20	+	−/+
CD79a	+	−/+
CD30	−	+ (100%)
CD15	−	+ (70%)
Cell type		
Lymphocytic-histiocytic (L&H)	+	−
Reed-Sternberg (RS)	−	+

Lymphocytic and histiocytic cells (or L&H RS cell variant) are seen in nodular lymphocyte-predominant subtype of HL (NLPHL) and are derived from germinal center (GC) or post (GC) B-cells. These cells retain the expression of B-cell antigens (CD19, 20, 22, 79a) and have productive immunoglobulin gene rearrangements.

RS cells of classical HL arise from GC B-cells but have crippling mutations that destroy the coding capacity of their functional IGV gene rearrangements. These RS cells always express CD30 and in approximately 70% patients also express CD15. CD20 is expressed in 6–10% patients. RS cells never express B-cells antigens like CD45, CD19, and CD79a. In a minority (2%) of patients with classical HL, RS cells display a cytotoxic T-lymphoid phenotype.

PATHOLOGIC CLASSIFICATION

The WHO classification of lymphomas divides HL into classical and NLPHL. The classical HL is further subdivided into four categories according to the number of RS cells, characteristics of the inflammatory milieu, and the presence or absence of fibrosis. These are described in **Table 3**. NLPHL constitutes 5–10% of all HL cases and has a better outcome than those with classical HL.

CLINICAL MANIFESTATIONS

Common presenting symptoms and signs of HL in children includes contiguous lymphadenopathy, and systemic or B symptoms. From 80% to 90% of children with HL usually present with painless, firm (rubbery) lymphadenopathy usually involving the cervical or supraclavicular group of lymph nodes. Axillary and inguinal lymph nodes are involved less frequently. Nearly 60% patients have an associated asymptomatic involvement of mediastinal lymph nodes. Depending upon location and size of mediastinal mass, some patients may present with symptoms and signs of dysphagia, airway obstruction (dyspnea, cough, stridor, and hypoxia) or the superior vena cava syndrome. Disease presenting below the diaphragm is rare and represents ~3% of all cases. From 15% to 20% of patients have noncontiguous extranodal involvement (stage IV) of lung, liver, bone, and bone marrow. Patients also exhibit immune system abnormalities especially involving cell-mediated immunity resulting in increased susceptibility to infections.

Patients with HL may present with nonspecific systemic symptoms such as fatigue, anorexia, and weight loss. Systemic symptoms classified as B symptoms that are considered important in staging include fever greater than 39°C for more than 3 days, weight loss greater than 10% over 6 months, or drenching night sweats. Patients with NLPHL are usually males younger than 10 years and generally present with slow growing, localized, nonbulky disease usually in axilla and inguinal regions without any B symptoms. Rarely, patients may present with autoimmune disorders such as autoimmune hemolytic anemia, thrombocytopenia, or neutropenia.

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of HL may be caused by a variety of other diseases. The differential diagnosis includes: (1) *Infections*: These include typical and atypical mycobacterial infections, HIV, EBV, and CMV; (2) *Other malignancies*: Such as non-Hodgkin lymphoma, soft tissue sarcoma, and nasopharyngeal carcinoma; (3) Autoimmune disorders like systemic lupus erythematosus (SLE).

EVALUATION

In addition to a thorough history and physical examination, the work-up of a patient with suspected HL includes disease confirmation and staging by the following tests.

Confirmatory Tests
Biopsy An excisional lymph node biopsy is mandatory for confirmation of diagnosis. Since lymph node architecture is important for histological classification, fine-needle aspiration cytology (FNAC) alone is not sufficient and not recommended.

Disease Staging
Imaging Chest X-ray, computed tomography (CT) scan of neck, chest, abdomen, and pelvis should be obtained. Contiguous nodal clustering or matting, focal mass lesion in a visceral organ, size on long axis greater than or equal to 2 cm or 1–2 cm with other suggestive clinical features favor lymphomatous involvement. Bulky peripheral (nonmediastinal) lymphadenopathy is generally accepted as aggregate nodal mass greater than 5–6 cm. Bulky mediastinal mass is defined as a transverse mediastinal diameter greater than one-third of maximum intrathoracic diameter on an upright posteroanterior (PA) chest radiograph.

Positron emission tomography (PET) scan Whole body PET scan using 18F-fluorodeoxyglucose activity has been shown to be a more sensitive radiographic modality than CT or gallium scanning and may identify more sites of initial disease and is more accurate in detecting viable HL in post-therapy residual masses. Concordance between PET and CT scans is generally high for nodal regions but lower for extranodal sites such as spleen, lung nodules, bone/bone marrow, and pleural/pericardial effusions. A rapid early response documented by significant reduction in disease volume and PET negativity at an early stage (after one or two cycles of chemotherapy) is associated with a favorable outcome. PET scanning should be performed at baseline and a minimum of 3 weeks postchemotherapy completion and 3 months postradiotherapy completion.

Bone marrow aspiration and biopsy It is done for patients with advanced disease (stage III/IV), B symptoms, bony involvement, and abnormal counts.

Supportive Investigations
These include complete blood counts, liver function tests, kidney function tests, erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase, serum albumin, and viral markers (HIV, HBsAg, anti-HCV).

Table 3 Histopathologic classification of classical Hodgkin lymphoma

WHO subgroup	Distinctive features	Relative frequency (%)
Lymphocyte rich	• Benign appearing lymphocytes with or without histiocytes • Few RS cells • No fibrosis	10–15
Nodular sclerosis	• Thickened capsule with proliferation of orderly collagenous bands that divide lymphoid tissue into nodules • Lacunar variant of RS cells	20–50
Mixed cellularity	• 5–15 RS cells/high power field • Fine fibrosis in interstitium • Focal necrosis may be present	20–40 Most common in children of developing countries
Lymphocyte depletion	• Abnormal cells with relative paucity of lymphocytes • Fibrosis and necrosis are common and diffuse	5–16

Abbreviation: RS cells, Reed-Steinberg cell.

Table 4 Modified Ann Arbor classification of Hodgkin lymphoma

Stage	Definitions
I	Involvement of a single lymph node (LN) region (I) or of a single extranodal organ or site (IE)
II	Involvement of two or more LN regions, on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more LN region on the same side of the diaphragm (IIE)
III	Involvement of LN regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ (IIIE) or both (IIISE)
IV	Noncontiguous involvement of one or more extralymphatic site with or without LN involvement
Annotations	**Definitions**
A	No B symptoms
B	At least one of the following within the last 6 months: • Unexplained weight loss > 10% • Unexplained persistent or recurrent fever > 38°C for 3 days • Drenching night sweats
X	Bulky disease (> 6 cm in diameter or mass > 1/3 rd of mediastinal) diameter
E	Extension to a single extralymphatic organ from contiguous nodal disease

Table 5 Prognostic factors and risk stratification in pediatric Hodgkin lymphoma

Study group	Low risk	Intermediate risk	High risk
Children's Oncology Group	• IA/IIA; no bulk or extranodal extension	• IA bulk or "E" extension • IIA bulk or "E" extension • IIB • IIA • IVA	• IIIB, IVB
German studies/Euronet PHL	• IA/B • IIA	• IIB • IIEA • IIIA	• IIEB • IIIEA/B • IIIB • IV
St Jude/ Stanford/ Dana-Farber	• IA/IIA no bulk	• IA bulk • IB • IIA bulk • IIB • III • IV	
Children's Cancer Group 5942	• IA/B patients no adverse features* • IIA patients no adverse features*	• IA/B patients with adverse features* • IIA patients with adverse features* • IIB • IIIA/B	• IV

* Adverse features include hilar lymphadenopathy, more than four sites of nodal disease, or bulky disease.

STAGING AND RISK STRATIFICATION

The Ann Arbor staging system with Cotswolds modification is the current staging system used for patients with HL (**Table 4**). In an attempt to identify subset of patients who require intensive therapy, most pediatric oncology groups use a risk-adapted treatment approach. While the specific definitions of low-, intermediate-, and high-risk disease may vary with group, most stratify patients based on stage, disease bulk, and systemic (B) symptoms (**Table 5**).

TREATMENT

The treatment of HL in children requires a delicate balance to maximize the treatment efficacy and minimize the risk for late toxicities associated with both radiation therapy (RT) and chemotherapy. A number of clinical trials have demonstrated that combining the two modalities allows for a decrease in dose and size of radiation field used and reduction in intensity/cumulative dose of chemotherapy, thus decreasing overall acute and late toxicities. While RT acts to control known tumor sites, chemotherapy aimed at occult disease outside the radiation field. This combined modality therapy produces a superior event-free survival. Response to therapy is one of the most robust prognostic factors in HL as in many other pediatric tumors. The concept of tailoring the extent as well as dose of radiotherapy and duration of chemotherapy based on response to therapy in HL is the focus of many recent and future trials. Hence, current standard of care for childhood HL is risk, gender and response adapted use of combination chemotherapy with or without low-dose involved-field RT (IFRT).

Chemotherapy

The contemporary chemotherapy regimens in HL combine non-cross-resistant agents wherein each agent is individually active against tumor but targets different cellular events to prevent drug resistance and have nonoverlapping toxicities, which allows delivery of each agent at the full dose. The commonly used chemotherapy regimens have been highlighted in **Table 6**. In contrast to adult HL, pediatric chemotherapy approaches have focused mainly at avoidance of late toxicity of chemotherapy and adapting the chemotherapy based on patients' gender. In attempt to avoid cardiac and pulmonary toxicity of ABVD, many investigators have evaluated regimens (like VAMP) devoid of anthracyclines, alkylators, and/or bleomycin. Such regimens such

Table 6 Commonly used chemotherapy regimens for children with Hodgkin lymphoma

Name	Drugs
COPP	Cyclophosphamide, vincristine, procarbazine, prednisone
COPDAC	Dacarbazine substituted for procarbazine in COPP
OPPA	Vincristine (Oncovin®), procarbazine, prednisone, adriamycin
OEPA	Vincristine, etoposide, prednisone, adriamycin
ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
COPP/ABV	Cyclophosphamide, vincristine, procarbazine, prednisone, adriamycin, bleomycin, vinblastine
VAMP	Vinblastine, adriamycin, methotrexate, prednisone
DBVE	Doxorubicin, bleomycin, vincristine, etoposide
ABVE-PC	Adriamycin, bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide
BEACOPP	Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, procarbazine

as VAMP are less toxic but are effective only in favorable risk HL, and not in intermediate- or high-risk HL. Similarly in an effort to decrease risk for male infertility, etoposide has been substituted for procarbazine (OEPA instead of initial OPPA).

Radiotherapy

Radiation has been used as an adjunct to multiagent chemotherapy especially in intermediate- or high-risk pediatric HL with the goal to reduce risk of relapse in initially involved sites and prevent toxicity associated with second-line chemotherapy. Doses of 15–25 Gy are typically used with modifications based on patients' age, presence of bulky or residual (postchemotherapy) disease. IFRT is the current standard of care in children in place of total nodal RT. While CT-based two-dimensional RT remains the standard technique for radiation delivery, three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) are often used in situations where the more conformal techniques would reduce dose to surrounding normal critical structures.

Recommendations for Treatment of Newly Diagnosed HL

The risk-adapted treatment for newly diagnosed pediatric HL has been depicted in **Table 7**. NLPHL is an uncommon subtype

Table 7 Risk-adapted treatment of newly diagnosed Hodgkin lymphoma in children

Risk group	5-year EFS (%)	5-year OS (%)
Low-risk disease		
• Four cycles of VAMP + LD-IFRT (if not in CR after 2 cycles) or without IFRT (if in CR post 2 cycles)		
• Four cycles of COP/ABV + LD-IFRT	92	98
• ABVE or ABVD (2–4 courses depending on response) followed by LD-IFRT		
• Two cycles of OEPA or OPPA + LD-IFRT (if not in CR after 2 cycles) or without IFRT (if in CR post 2 cycles)		
Intermediate-risk disease		
• Six cycles of COPP/ABV + LD-IFRT		
• Four cycles of chemotherapy (ABVD) + LD-IFRT in bulky/residual disease	85	95
• ABVE-PC (3–5 courses depending on response) with/without LD-IFRT		
• Two cycles of OPPA (for females) or OEPA (for males), followed by 2 cycles of COPP (for females) or COPADAC (for males) + LD-IFRT		
High-risk disease		
• ABVE-PC (3–5 courses depending on response) followed by LD-IFRT		
• Two cycles of OPPA (females) or OEPA (males), followed by 4 cycles of COPP (for females) or COPADAC (for males) + LD-IFRT	83	94
• Two cycles of cytarabine/etoposide, COPP/ABV, and CHOP + LD-IFRT		
• Four cycles of BEACOPP with subsequent dependent upon response. Rapid responders: 4 cycles of COPP/ABV without IFRT (for females) or 2 cycles ABVD with IFRT (for males). Slow responders: 4 additional cycles of BEACOPP with IFRT		

and presents with more indolent disease than classical HL. The patients with stage I/II NLPHL without B symptoms are treated with less intensive therapy than patients with classical HL. In contrast, patients with stage III/IV are treated on similar protocols as those of classical HL. Given the indolent nature of NLPHL and potential chemotherapy-related morbidities and mortalities, the attempt is at de-escalating the treatment intensity. In efforts towards these, various groups have studies COPP/ABV, and VAMP without the use of RT for reducing long-term effects of treatment.

Treatment of Relapsed/Refractory Disease

Refractory (resistant) HL is defined as those patients who fail to obtain a complete response with initial therapy, or those who relapse within 3 months from the end of therapy. In contrast, relapsed HL describes the reappearance of HL greater than 3 months after attainment of a complete response. Most relapses occur within first 3 years. Relapsed patients can be classified into two groups for prognostication and treatment planning.

Low-risk (Favorable) Group

Children with localized late relapse (≥ 12 months after completing therapy) after limited therapy with chemotherapy alone and/or IFRT have a high likelihood of achieving long-term survival following treatment with more intensive conventional chemotherapy alone. Intensive non-cross-resistant regimens using agents not part of initial treatment such as cytarabine, platinum-based compounds (cisplatin/carboplatin), ifosfamide, etoposide, vinorelbine, gemcitabine and vinblastine have been used. Approximately, two-thirds of patients can be salvaged with second-line chemotherapy.

High-risk Group

Children who develop relapse within 1 year of completing the therapy require aggressive salvage chemotherapy and consolidation with autologous hematopoietic stem cell transplantation (HSCT) with survival rates ranging between 45% and 70%. Salvage rates for patients with primary refractory HL are poor even with autologous HSCT and range from 20% to 40%. Patients who fail autologous HSCT and for patients with chemoresistant disease, allogeneic HSCT has been used with encouraging results. Brentuximab, an anti-CD30 monoclonal antibody has been evaluated in adults with relapsed/refractory HL and has shown promising response rates of 50–70% in recent phase I/II studies.

Follow-up and Late Effects

Current 5-year survival for HL is approximately 90% with higher rates reported in younger populations. The long-term survivors of HL may suffer from an array of unwanted side effects. Mortality in the first 15 years after diagnosis of HL relates to the primary disease and following that to second cancers (SMNs) and cardiovascular disease. In a large retrospective study of pediatric cancer survivors including 1,876 HL survivors, at 25 years of follow-up the cumulative incidence rates of total (grade 1–5) and severe (grades 3–5) chronic medical conditions in HL survivors were approximately 75% and 40% respectively. The late complications primarily include impaired growth of bones and soft tissues, thyroid dysfunction, gonadal dysfunction, cardiopulmonary toxicity and second malignancies. Hence, all

children treated with HL should be closely followed for relapse as well as late effects. Imaging is not recommended for routine follow-up, as recent studies have shown that most relapses can be detected based on symptoms, laboratory and physical findings without any incremental value of imaging.

CONCLUSION

Pediatric HL is one of the most treatable childhood malignancies with greater than 90% cure rates. Risk and response adapted combined modality therapy is the current standard of care. Most of the current trials are exploring strategies of reducing acute and long-term treatment related adverse effects while maintaining the excellent cure rates.

MORE ON THIS TOPIC

Diehl V. Hodgkin's disease—from pathology specimen to cure. N Engl J Med. 2007;357:1968-71.

Dinand V, Arya LS. Epidemiology of childhood Hodgkin's disease: is it different in developing countries? Indian Pediatr. 2006;43:141-7.

Glaser SL, Hsu JL. Hodgkin's disease in Asians: incidence patterns and risk factors in population-based data. Leuk Res. 2002;26:261-9.

Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med. 2003;349:1324-32.

Naresh KN, Johnson J, Srinivas V, et al. Epstein-Barr virus association in classical Hodgkin's disease provides survival advantage to patients and correlates with higher expression of proliferation markers in Reed-Sternberg cells. Ann Oncol. 2000;11:91-6.

Swerdlow SH, Campo E, Harris NL Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press; 2008.

Yeole BB, Advani SH, Sunny L. Epidemiological features of childhood cancers in greater Mumbai. Indian Pediatr. 2001;38:1270-7.

IN A NUTSHELL

1. Hodgkin lymphoma is a B-lineage lymphoma characterized by presence of clonal RS cells or L&H cells.
2. The incidence of HL is bimodal in developed countries with the early peak occurs in young adults followed by a late peak in elderly and trimodal distribution in developing countries with the first peak occurring before adolescence.
3. As per WHO classification, HL is classified into classical and NLPHL.
4. Majority of children with HL present with painless, firm, rubbery lymphadenopathy usually involving cervical/supraclavicular group.
5. Systemic symptoms classified as B symptoms that are considered important in staging include fever greater than 39°C for more than 3 days, weight loss greater than 10% over 6 months, or drenching night sweats.
6. Confirmation of diagnosis is by lymph node biopsy and FNAC alone is not sufficient.
7. Positron emission tomography scan has been found to be better than conventional imaging in staging, response assessment and prognostication.
8. The current standard of care for childhood HL is risk, gender and response adapted use of combination chemotherapy with or without low-dose IFRT.
9. The commonly used chemotherapy regimens include ABVD, VAMP, OEPA, and OPPA. Radiation modalities employed include CRT, IFRT, and IMRT.
10. The 5-year survival for HL is approximately 90% but 75% long-term survivors of HL may suffer from an array of unwanted side effects including second cancers (SMNs) and cardiovascular disease. Hence, survivors should be followed up closely for life.

Chapter 45.7
Non-Hodgkin Lymphoma
Nirav Thacker, Vikramjit S Kanwar, Tipu Nazeer

Lymphomas are the third most commonly diagnosed childhood cancer, and approximately half of these tumors are non-Hodgkin lymphoma (NHL). In India, precise numbers are hard to obtain, but it is estimated that at least 3,000 children develop NHL each year. Each subtype of NHL arises from a lymphoid progenitor cell arrested at a particular stage of differentiation, with distinct pathologic, immunologic and clinical characteristics. Unlike in adults, NHL in children is a systemic disease that usually presents as diffuse, aggressive cancer which easily spreads through the bloodstream, requiring a unique staging system and aggressive treatment. When treated promptly at a center that specializes in childhood cancer, using contemporary chemotherapy protocols and appropriate supportive care, pediatric NHL can achieve a cure rate of 80% or greater.

INCIDENCE AND EPIDEMIOLOGY

In India, the annual incidence of NHL in both sexes is around 5 per million children (0–14 years of age), similar to the incidence in the developed world. However, as a proportion of reported childhood cancers, lymphoma makes up 12–25% of all childhood cancers, unlike the 10% reported from Europe and the United States, making lymphoma the second most common childhood cancer in India. In India, the reported incidence of Hodgkin lymphoma (HL) may exceed NHL, a pattern opposite to that usually seen in Europe and the United States. Some of these differences are secondary to the high incidence of HL reported in male children in North India, suggesting that reporting bias may be a partial explanation. Amongst pediatric NHL patients in India, the proportion of T-cell lymphoblastic lymphoma (LL) and diffuse large B-cell lymphoma (DLBCL) is much higher than mature B-cell (Burkitt and Burkitt-like) lymphoma (BL), which may again reflect reporting bias, as opposed to genuine biologic differences. NHL is uncommon in children less than 5 years of age, with BL most often seen in younger children. DLBCL or anaplastic large cell lymphoma (ALCL) are more common in older children and teenagers. The incidence of T-cell LL is constant throughout childhood. Pediatric NHL is more common in males than females in all age groups (3:1), with the exception of primary mediastinal B-cell lymphoma (PMBCL), in which the incidence is almost the same in males and females. The incidence and frequency of histologic subtypes of NHL vary in different parts of world, and even within different parts of the same country. In equatorial Africa, BL accounts for half of childhood cancers, whereas NHL is rare in Japan.

ETIOLOGY

The etiology of pediatric NHL is largely unknown. Known risk factors are immunodeficiency, both congenital (Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, ataxia telangiectasia and severe combined immunodeficiency) and acquired (human immunodeficiency virus infection [HIV] or post-transplant immunodeficiency), which increases the risk of NHL 100-fold as compared with age-matched controls. Epstein-Barr virus (EBV) is associated with most cases of NHL seen in the immune-deficient population. While endemic BL in Africa is almost always associated with EBV, only 15% of cases of sporadic BL in Europe or the United States have EBV detectable in tumor tissue. Therapy-related NHL in children is extremely rare.

PATHOLOGY

Pediatric NHL consists of cancers derived from immature and mature lymphoid cells of either B-cell or T-cell lineage. Unlike adults, more than 95% of pediatric patients with NHL have high grade neoplasms. The World Health Organization (WHO) has classified pediatric NHL on the basis of phenotype (i.e., B-lineage and T-lineage or natural killer [NK] cell lineage) and differentiation (i.e., precursor-lymphoblastic vs. mature). Although nearly all subtypes of NHL have been described in children, almost all cases commonly seen are limited to four subtypes, namely BL, LL, DLBCL, and ALCL (**Fig. 1**). The pathology of pediatric NHL is easily confused in inexperienced hands, especially if hematoxylin and eosin (H&E) staining alone is used to make a diagnosis.

Burkitt Lymphoma
Burkitt lymphoma accounts for around a third of all pediatric NHL. BL is characterized by intermediate sized homogeneous cells with round to oval nuclei, multiple nucleoli and modest basophilic cytoplasm, which appears vacuolated due to lipid droplets. The tumor cells have a high mitotic activity, and tissue sections often show classical *starry sky* appearance that results from reactive macrophages scattered among malignant cells, engulfing debris from rapidly dividing tumor cells (**Fig. 2**).

Burkitt lymphoma also includes the related histologic subtype termed as *Burkitt-like* or *atypical Burkitt* lymphoma; the exact distinction between them is still controversial, though cytogenetic evidence of c-myc rearrangement is taken as the gold standard of BL. This distinction is of less concern clinically as Burkitt-like lymphoma is treated with the same aggressive chemotherapy regimen as BL.

Lymphoblastic Lymphoma
Lymphoblastic lymphoma accounts for 15–20% of pediatric NHL with more than 90% having a T-cell lineage, with precursor-B LL being less than 10%. Gene profiling studies suggest LL is biologically distinct from the corresponding acute leukemias despite the blasts having morphologic similarities. T and B lymphoblasts are hard to distinguish by cytology and are only identified by immunophenotyping

Diffuse Large B-Cell Lymphoma
Diffuse large B-cell lymphoma belongs to the family of mature B-cell neoplasm accounting for 10–20% of pediatric NHL. Morphologically, DLBCL is characterized by large lymphoid cells, with variably pale to granular cytoplasm which is more abundant than in BL, and the lymph node architecture is diffusely effaced (**Figs 3A and B**). The numerous morphological subtypes of DLBCL (e.g., centroblastic, immunoblastic, etc.) are similar in clinical behavior and subclassification is no longer recommended by WHO.

With the exception of PMBCL, pediatric and adult DLBCL are biologically distinct. Pediatric DLBCL have a high mitotic rate on Ki-67 staining with almost all having germinal center B-cell like (GCB) phenotype. Around 30% of patients younger than 14 years with diffuse large B-cell lymphoma have a gene signature similar to BL.

Anaplastic Large Cell Lymphoma
Anaplastic large cell lymphoma accounts for 10–15% of cases of pediatric NHL. Although majority (80%) of ALCL have a
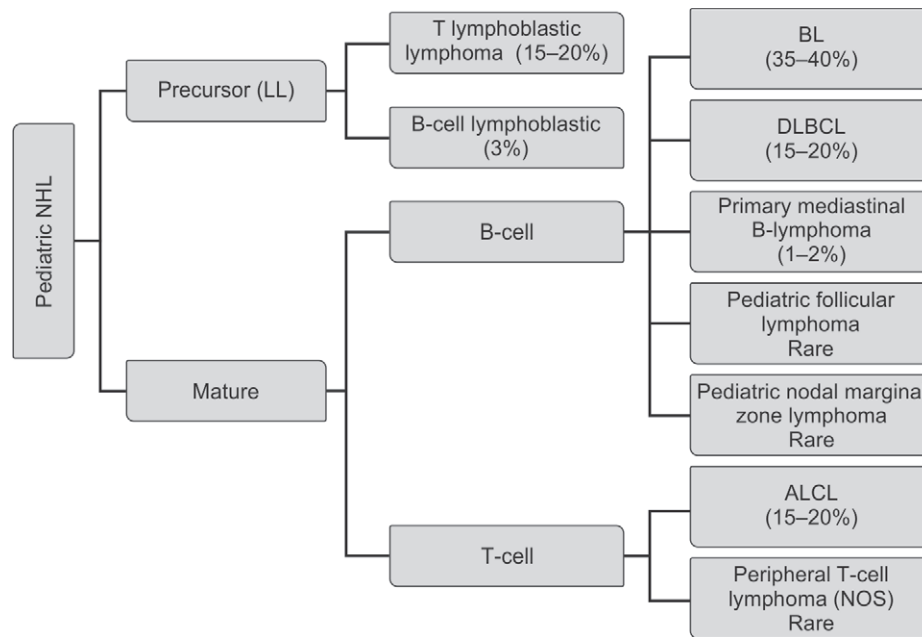
Figure 1 Main subtypes of pediatric non-Hodgkin lymphoma (NHL) (WHO, 2008)
Abbreviations: LL, lymphoblastic lymphoma, DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; BL, Burkitt lymphoma.
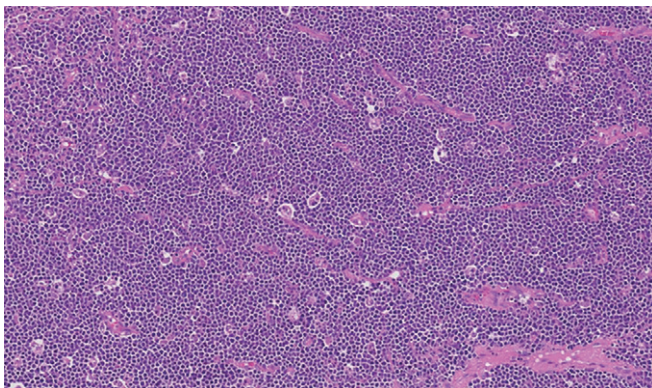
Figure 2 Burkitt lymphoma: Diffuse proliferation of intermediate sized cells with interspersed tingible body macrophages creating a starry sky appearance
Source: T Nazeer

mature T cell immunophenotype, 20% do not have any specific immunophenotype (non-T/B/NK cell) and are null cell type. There are several morphological variants of ALCL, the majority being anaplastic/classical (> 75%) with large pleomorphic, multinucleated or horseshoe like hallmark cells (**Fig. 4**). The remaining are either lymphohistiocytic variant with plenty of benign histiocytes and sparse neoplastic cells, or small cell variant with predominantly small neoplastic cells and few hallmark cells, and both variants are associated with more aggressive disease and higher rates of treatment failure. Despite morphological diversity, ALCL have a consistent expression of CD30 and frequent expression of epithelial membrane antigen (EMA). The majority (90%) of pediatric ALCL cases have a chromosomal rearrangement of t(2;5) involving the *ALK* gene.
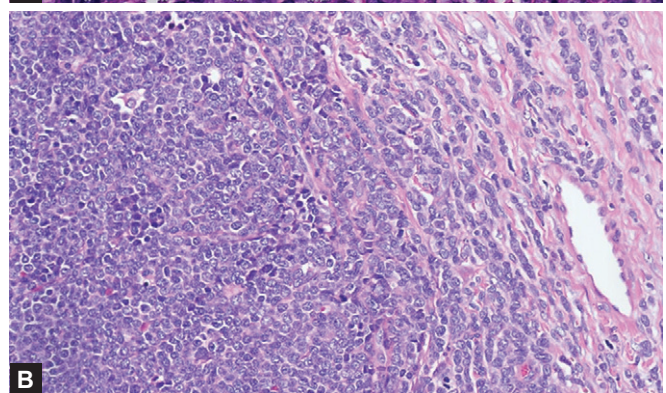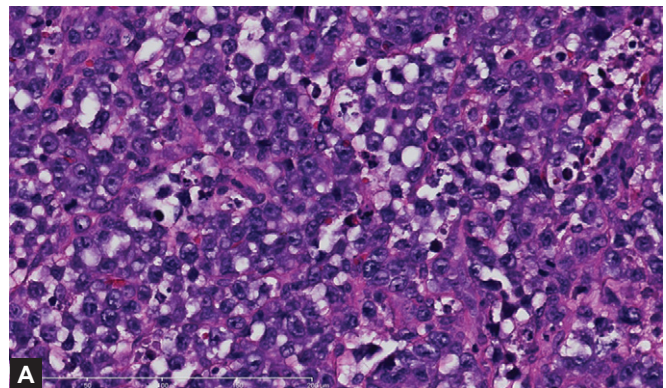
Figures 3A and B (A) Large B-cell lymphoma: Diffuse proliferation of large immunoblasts/centroblasts; (B) Large B-cell lymphoma: Nodal paracortical and capsular Indian file involvement by lymphoblasts. T and B lymphoblasts are indistinguishable by cytology and are only identified as such by immunophenotyping
Source: T Nazeer
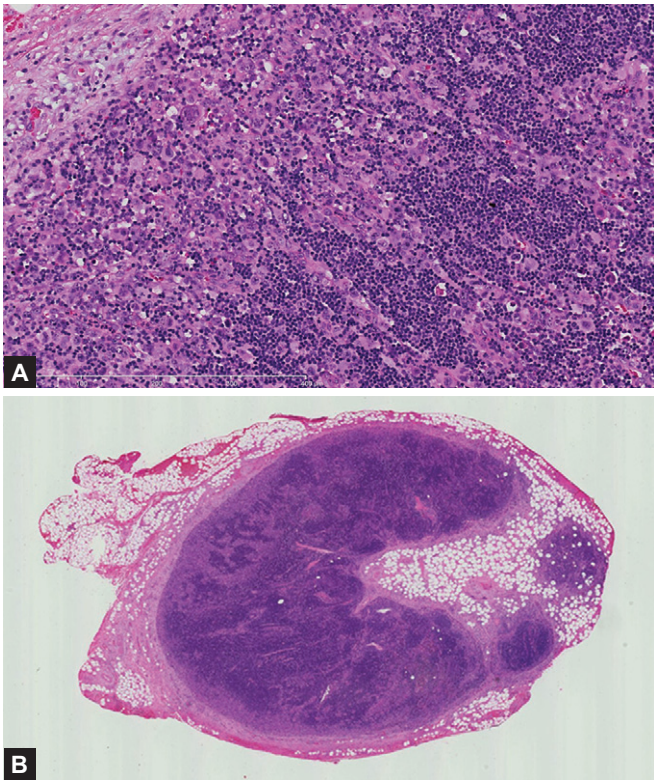
Figures 4A and B (A) Anaplastic large cell lymphoma (ALCL) high power: Subcapsular sinus expanded by large anaplastic cells including Reed-Sternberg-like cells in anaplastic large cell lymphoma; (B) Anaplastic large cell lymphoma (ALCL) low power: Typical nodal sinusoidal involvement by anaplastic large cell lymphoma
Source: T Nazeer

Immunodeficiency associated NHL NHL associated with immunodeficiency usually have a B-cell phenotype (90%), which is more often large B-cell histology than Burkitt, with only 10% being mature peripheral T-cell lymphomas. Post-transplant lymphoproliferative diseases are classified according to WHO nomenclature as early lesions, polymorphic or monomorphic.

Rare Lymphomas

Follicular lymphoma (FL) and MALT lymphomas are indolent B-cell lymphomas which are extremely rare in children (< 0.5%), present with localized disease and have excellent outcomes.

CLINICAL FEATURES

Pediatric NHL is a heterogeneous group of neoplasms with a diverse presentation depending on the histological type, primary site and extent of disease (**Table 1**). Some children with NHL, like the majority of adults, will present with lymph node disease. However, most children typically have extranodal disease involving virtually any lymphoid tissue, commonly the mediastinum (26%), abdomen (30%), or head and neck (30%). Pediatric NHL being aggressive, two-thirds of children will have locally advanced or metastatic disease (Stages III and IV) at time of diagnosis. Being rapidly growing tumors, symptoms develop quickly over a few weeks and a substantial number of patients present with oncological emergencies requiring immediate intervention (**Table 2**). Signs and symptoms are usually due to local effects attributable to bulk of tumor mass, regional effects due to compression of surrounding structures, and metastasis (bone marrow, central nervous system [CNS]). CNS involvement presents with CNS symptoms such as headaches and/or cranial nerve palsy. Bone marrow involvement may lead to pancytopenia.

Burkitt Lymphoma

There is male predominance and peak age of presentation is 4–6 years. BL can present with a palpable abdominal mass or pain in the periumbilical region or right iliac fossa mimicking appendicitis. Nausea, vomiting and weight loss are other presenting features. BL in endemic areas may present with a jaw mass. Signs and symptoms of intestinal obstruction can occur due to direct compression of bowel lumen or intussusception. BL should always be considered in the differential diagnosis of intussusception in children older than 2 years of age. Occasionally, BL may present with bowel perforation, which may also develop after the initiation of chemotherapy. Epidural masses can present with recent onset paraparesis/paraplegia and bladder or bowel involvement. Spontaneous tumor lysis is common with BL and needs prompt management. Burkitt leukemia is BL with more than 25% blasts in the bone marrow, and may present like leukemia with

Table 1 Common subtypes of pediatric non-Hodgkin lymphoma (NHL)

Histology	Immunophenotype	Clinical presentation	Cytogenetics	Genes commonly affected
Burkitt/Burkitt-like lymphomas	Mature B-cell CD10+,CD20+, sIg+	Intra-abdominal mass, tonsillar mass Bone marrow involvement with cytopenias, CNS involvement with cranial nerve palsy, jaw swelling (endemic)	t(8;14), t(2;8), t(8;22)	*C-MYC*
Diffuse large B-cell lymphoma	Mature B-cell CD10+ or CD10-, CD19+, CD20+, CD22+	Lymph node and abdominal masses, bone swelling Primary CNS involvement (when associated with immunodeficiency)		*C-MYC*
Lymphoblastic lymphoma	Pre-T-cell CD3+, TdT+, CD7+,	Mediastinal mass with respiratory distress, lymph node masses, bone marrow involvement with cytopenias	t(1;14), t(11;14), t(10;14), t(7;19) t(1;7)	*TAL1, TCRAO, RHOMB1, HOX11*
	Pre-B-cell CD10+, CD79a+	Skin and soft tissue nodules		
Anaplastic large cell lymphoma	T-cell or null cell type CD30+ (Ki-1+), EMA +ve	Skin nodules, lymph node masses, bone swelling	t(2;5)	*ALK, NPM*
Primary mediastinal large B-cell	B-cells of medullary thymus CD10+ or CD10-, CD19+, CD20+, CD22+, CD79a	Mediastinal mass	Del 9q	*C-REL*

Table 2 Oncologic emergencies in pediatric non-Hodgkin lymphoma (NHL)

Oncologic emergency	Cause(s)
Cardiorespiratory	
Superior vena cava syndrome	Mediastinal mass
Acute airway obstruction	Mediastinal, pharyngeal mass
Cardiac/respiratory compromise	Massive pericardial, pleural, peritoneal effusion
Neurological	
Paraplegia	Epidural mass
Raised intracranial pressure, focal neurological deficit	Intracranial mass or meningeal involvement
Gastrointestinal and hepatobiliary	
Obstructive jaundice/pancreatitis	Retroperitoneal mass
Intussusception, intestinal obstruction/perforation, gastrointestinal bleeding	Intestinal mass
Renal	
Ureteral obstruction, unilateral/bilateral hydronephrosis	Retroperitoneal/pelvic mass
Metabolic	
Tumor lysis syndrome	High tumor burden such as Burkitt lymphoma or T-cell lymphoma-leukemia

fever, pallor, hepatosplenomegaly, peripheral lymphadenopathy and pancytopenia. CNS involvement occurs in up to 8% of patients with BL.

T-Cell Lymphoblastic Lymphoma

T-cell lymphoblastic lymphoma is more common in males, incidence being stable across all pediatric age groups with a median age of diagnosis of 12 years. Around 75% of patient of T-LL present with cervical lymphadenopathy, anterior mediastinal mass and pleural effusion, which manifests clinically as cough, orthopnea, dyspnea, stridor, wheeze, swelling and superior vena cava syndrome (**Figs 5A and B**). Patients with large mediastinal

masses are at increased risk of respiratory or cardiac arrest during general anesthesia or heavy sedation.

Hemodynamic compromise could be presenting symptom in presence of pericardial or pleural effusion. Subdiaphragmatic disease is usually in form of kidney deposits, retroperitoneal lymphadenopathy and hepatosplenomegaly. Patients having bone marrow involvement (more than 25%) are classified and managed like acute leukemia. CNS involvement is rare and is seen in 3% of T-LL. Of note, children with B-LL tend to have a more localized disease limited to skin, bone, and peripheral lymph nodes. Cutaneous lesions typically occur in the scalp as large, discolored masses. Bone marrow involvement is uncommon.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma has a variable presentation in children. Patients may present with a rapidly enlarging mass, usually nodal enlargement in the neck or abdomen. However, extranodal involvement of bone is also common. PMBCL is a distinct entity, typically diagnosed in young adult females, with biology similar to adult DLBCL. Patient often presents with superior vena cava (SVC) syndrome. The tumor, being locally invasive, can present with pericardial effusion and lung involvement. Primary DLBCL of the brain may be seen in immunocompromised patients.

Anaplastic Large Cell Lymphoma

The median age of presentation is 12 years, with two-thirds of cases presenting with advanced disease. Children with ALCL usually have constitutional symptoms of fever and weight loss. The most frequent sites of involvement in systemic ALCL are peripheral nodes, mediastinal adenopathy, and extranodal sites including skin (most common), lung, soft tissue, and bone. Classically waxing and waning of skin disease is known in systemic ALCL. Bone disease is also common and is multifocal in as many as 10% of patients. Patients who have the small cell variant of ALK positive ALCL may present with peripheral blood involvement akin to leukemia. CNS involvement is rare.

DIFFERENTIAL DIAGNOSIS

The signs and symptoms of NHL in children and adolescents may be caused by a variety of diseases and the differential diagnosis includes other malignant, infectious, surgical and inflammatory diseases (**Box 1**).
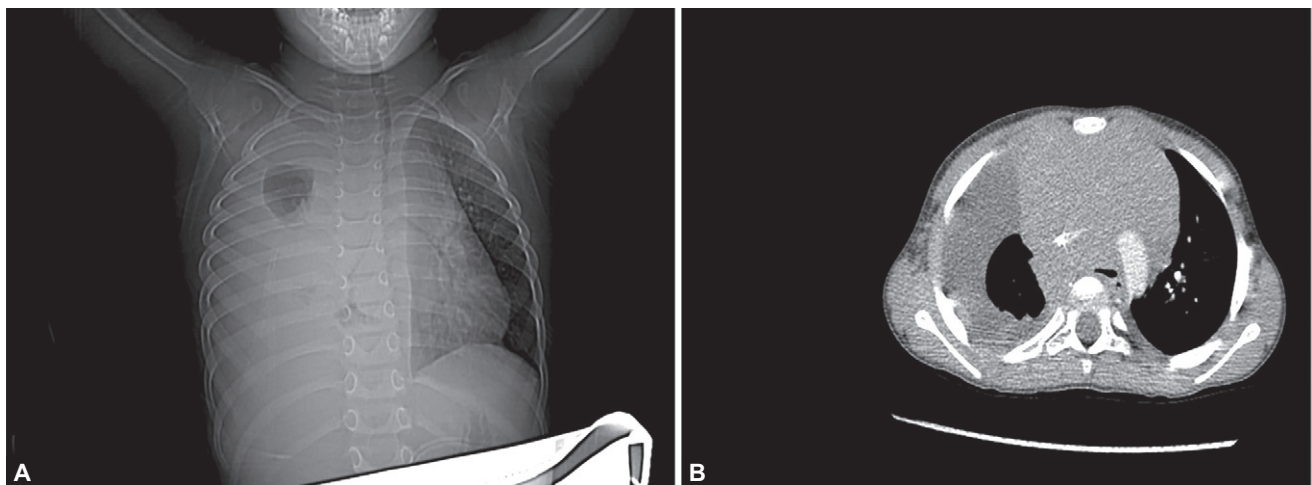
Figures 5A and B A 4-year-old child with T-cell lymphoblastic lymphoma (T-LL), presenting with large mediastinal mass with severe airway narrowing and displacement. The diagnosis was made on pleural aspirate after emergent steroids were commenced, and the child is in remission 5 years after completing 24 months of T-LL chemotherapy
Source: V Kanwar

The diagnostic considerations in patients with mediastinal masses include nonmalignant conditions like histoplasmosis, sarcoidosis. Malignancies involving the mediastinum include Hodgkin disease, germ cell tumor and thymic carcinoma (typically involving the anterior mediastinum), and neuroblastoma (involving the posterior mediastinum).

APPROACH TO DIAGNOSIS

Obtaining a quick and accurate diagnosis is the key to a successful outcome. Once clinical presentation suggestive of NHL is found, such as anterior mediastinal mass with or without a pleural effusion, firm nontender progressive adenopathy, or an unexplained right lower quadrant intra-abdominal mass, diagnostic material should be obtained expeditiously. An X-ray or a computed tomography (CT) scan will clarify the dimensions of any primary mass and the best place to obtain a surgical biopsy. In all cases, pathology or cytology specimens obtained should be reviewed by an experienced hematopathologist. Despite the unreliability of fine needle aspiration cytology (FNAC), it is not uncommon to find FNAC performed for screening. If clinical suspicion is high, it is crucial to obtain histopathology for diagnosis, with immunohistochemistry for confirmation. Because pediatric NHL is rare, patients may present with advanced disease, which means that supportive care may need to be provided even as diagnostic work-up is underway.

EVALUATION OF CHILDREN WITH NON-HODGKIN LYMPHOMA

Blood Investigations

Complete blood count is usually normal; pancytopenia is seen with marrow involvement. Uric acid, calcium, phosphate, and electrolytes are done as a part of tumor lysis syndrome (TLS) screen (TLS parameters). Renal and liver function tests are deranged if hepatobiliary or renal system is involved; lactate dehydrogenase (LDH) indicates tumor burden and is a prognostic marker.

Diagnostic Investigations

Tissue Diagnosis

Biopsy (open/image guided) depending on the site of involvement (abdominal mass, extranodal site, lymph node). If the patient's clinical condition is unstable, the diagnosis should be made with the use of less invasive procedures (percutaneous fine-needle aspiration or biopsy of a peripheral lymph node or large abdominal mass, or examination of cerebrospinal, pleural, or peritoneal fluid or bone marrow). FNAC may be performed as a screen but it is unreliable, and not recommended as a diagnostic test.

Immunophenotype

Identify the subtype of NHL as shown in **Table 1**. It can be done by immunohistochemistry on the fixed tissue or by flow cytometry on pleural fluid or involved bone marrow.

Cytogenetic Studies

To identify subtype and prognostic implication.

Staging Investigations

These involve bone marrow biopsy and aspiration, cerebrospinal fluid (CSF) cytology, and imaging to see extent of disease and response assessment. Whole-body CT is the imaging modality of choice to rapidly determine tumor extent and help stage the disease. Magnetic resonance imaging (MRI) is helpful in children with paraspinal mass to accurately determine extent of intraspinal extension. Positron emission tomography (PET) scan of whole body is helpful for staging and response evaluation.

Staging

The modified Ann Arbor staging classification does not adequately reflect prognosis in pediatric NHL, and Murphys staging (St Jude Children's Research Hospital) is the most widely used staging scheme for this age-group (**Table 3**). There is marked difference in the intensity and duration of therapy, as well as the prognosis, between patients with limited disease (stage I or II) and advanced disease (stage III or IV).

Table 3 Murphy staging system for pediatric non-Hodgkin lymphoma (NHL)

Stage I
• A single tumor (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen
Stage II
• A single tumor (extranodal) with regional node involvement
• Two or more nodal areas on the same side of the diaphragm
• Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm
• A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable
Stage III
• Two single tumors (extranodal) on opposite sides of the diaphragm
• Two or more nodal areas above and below the diaphragm
• Any primary intrathoracic tumor (mediastinal, pleural, or thymic)
• Extensive primary intra-abdominal disease
• Any paraspinal or epidural tumor
Stage IV
• Any of the above findings with initial involvement of the central nervous system, bone marrow, or both

Table 4 Standard treatment options for high-stage B-cell non-Hodgkin lymphoma (NHL)

	Stratum	Disease manifestations	Treatment
FAB/LMB-96 International Study COG-C5961 (FAB/LMB-96)	A	Completely resected stage I and abdominal stage II	Two cycles of chemotherapy
	B	Multiple extra-abdominal sites	Prephase + four cycles of chemotherapy (reduced intensity arm)
		Non-resected stage I and II, III, IV	
		Marrow < 25% blasts	
		No CNS disease	
	C	Mature B-cell ALL (> 25% blasts in marrow) and/or CNS disease	Prephase + eight cycles of chemotherapy (full intensity arm)
BFM Group	R1	Completely resected stage I and abdominal stage II	Two cycles of chemotherapy
	R2	Non-resected stage I/II and stage III with LDH < 500 IU/L	Prephase + four cycles of chemotherapy (4 hourly methotrexate infusion)
	R3	Stage III with LDH 500–999 IU/L	Prephase + five cycles of chemotherapy (24 hourly methotrexate infusion)
		Stage IV, B-cell ALL (> 25% blasts) and LDH < 1,000 IU/L	
		No CNS disease	
	R4	Stage III, IV, B-cell ALL with LDH > 1,000 IU/L	Prephase + six cycles of chemotherapy (24 hourly methotrexate infusion)

(Adapted from www.cancer.gov)
Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; CNS, central nervous system; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphomas.

Risk Stratification

The cooperative oncology groups FAB/LMB (French, American and British) and German Berlin-Frankfurt-Munster (BFM) groups have both risk stratified B-NHL for treatment planning, incorporating the stage, LDH, extent of surgical resection and extent of bone marrow or CNS involvement (**Table 4**). In B-NHL; adolescent age, PMBCL subtype, involvement of CNS with bone marrow, high LDH, and poor response to chemotherapy prophase (< 20% reduction in tumor burden) are all associated with poor prognosis. Secondary cytogenetic abnormalities, including gain of 7q or deletion of 13q in BL and del 6q in LL have been shown to be adverse factors. In ALCL, recent studies suggest that involvement of mediastinum, viscera (lung, spleen and/or hepatic disease) and skin is associated with a poorer outcome. Although monitoring of residual clonal lymphoma cells in the blood and/or bone marrow by means of aberrant immunophenotype or polymerase chain reaction (PCR) based technique is a potential tool for evaluating disease extent or treatment response in childhood ALCL and BL, it is not routinely used.

MANAGEMENT

Principles of Management

Childhood NHL is an extremely chemosensitive disease. Surgery plays a very limited role, mainly for arriving at a diagnosis, or for emergency management of obstruction or perforation. Radiation of primary sites is used very rarely in emergency situations, such as a large mediastinal mass causing airway obstruction. Multiagent chemotherapy directed to the histologic subtype and stage of the disease remains the cornerstone of therapy.

Emergency Management

Pediatric NHL can have rapid growth and a short doubling time, sometimes as short as 24 hours seen with BL. Life-threatening complications may develop as a result of physical compression of tumor masses on vital structures. In addition, high cell turnover in a large tumor results in biochemical disturbances (TLS), which needs to be anticipated and promptly addressed with adequate hydration and the use of allopurinol or rasburicase (urate oxidase). A steroid prophase in many regimens helps to achieve tumor control without increasing the risk of clinical deterioration during initiation of therapy.

Patients with large mediastinal masses are at risk of cardiorespiratory arrest, and should be started on empirical prednisone for up to 48 hours before biopsy at 60 mg/m^2/day and monitored in an intensive care unit, in propped-up lateral position. Emergent radiation therapy to the mediastinum to 600 cGy may be needed. A diagnostic biopsy may be deferred briefly until the patient is stable enough to undergo a procedure safely; examination of blood, a peripheral lymph node or of pleural or pericardial fluid may offer a way to promptly obtain diagnostic material obviating the need for riskier mediastinal biopsy.

Treatment of Lymphoblastic Lymphoma

Many studies including the seminal Children's Oncology Group (COG) trial that randomized all children with NHL to be treated with short duration pulse intensive COMP regimen (cyclophosphamide, vincristine, methotrexate [MTX], and prednisone) or to a long duration modified LSA$_2$L$_2$ regimen (used for acute lymphoblastic leukemia) have shown that LL fare better when treated with a leukemia-like regimen whereas B-cell NHL did better with short duration COMP. Similarly, POG demonstrated that lymphoma like protocol (CHOP) followed by maintenance chemotherapy with mercaptopurine and MTX resulted in long-term event-free survival (EFS) of only 65% in children with early LL. Thus, the chemotherapy regimen of choice for pediatric lymphoblastic lymphoma (both B and T-cell) is combination chemotherapy based on regimens used for acute lymphoblastic leukemia (ALL). With this approach, children with early stage (I or II) or advanced stage (III or IV) lymphoblastic lymphoma achieve long-term

survival rates of more than 90% and more than 80%, respectively. The value of nelarabine in higher stage T-cell LL is still being determined in a randomized phase III trial whose outcome is awaited.

In current era of intensive CNS-directed therapy with high-dose MTX combined with intrathecal therapy, cranial irradiation can be safely omitted in the majority of patients with its use limited to the few patients who present with frank CNS disease (< 5% of children). Irradiation of primary sites such as mediastinum has not been shown to improve outcome when added to chemotherapy. Even in patients with testicular disease at diagnosis, testicular radiation is only indicated for residual disease after systemic therapy incorporating high-dose MTX.

Treatment of Mature B-cell NHL (Burkitt Lymphoma and DLBCL)

Results from cooperative group studies suggest that with similar therapy there is no difference in outcome between pediatric BL and DLBCL and they should be treated with the same approach. In B-NHL, in view of high growth fraction and short doubling time; short, pulse-intensive, multiagent chemotherapy is given in courses of 3–5 days with a schedule characterized by fractionation or continuous infusion of drugs. To prevent rapid regrowth, courses are administrated at short intervals. Treatment intensity is adapted to tumor burden (stage, LDH level, bone marrow involvement, CNS involvement) and response to COP prephase.

Treatment of Limited Stage B-NHL

Patients with stage I and II disease have an excellent prognosis, regardless of histology. A children's cancer group study demonstrated that pulsed chemotherapy with COMP administered for 6 months for low-stage (stage I or II) non-lymphoblastic NHL was equivalent to 18 months of therapy with radiation to sites of disease, resulting in more than 85% disease-free survival (DFS) and more than 90% overall survival (OS). A pediatric oncology group (POG) study tested 9 weeks of short, pulsed chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without radiation to involved sites and with or without 24 weeks of maintenance chemotherapy, and the results showed no benefit of radiation or maintenance chemotherapy, but the survival for non-lymphoblastic lymphoma was superior to that of lymphoblastic lymphoma (90% vs. 60%).

For low-stage mature B-cell NHL, DFS is about 95%. The BFM group has treated risk group R1 (completely resected disease) with two cycles of multiagent chemotherapy (NHL-BFM-90 and NHL-BFM-95). For unresected stage I/II disease (R2), patients received a cytoreductive phase followed by five cycles of chemotherapy. In the NHL-BFM-90 study, it was shown that reducing the dose of MTX did not affect the results for low-stage disease. In NHL-BFM-95, it was demonstrated for low-stage disease that prolonging the duration of MTX infusion did not improve outcome. The French Society of Pediatric Oncology (SFOP) and French-American-British (FAB) studies treated all completely resected stage I and abdominal stage II (group A) with two cycles of multiagent chemotherapy, without intrathecal chemotherapy (COG-C5961 [FAB/LMB-96]).

Treatment of Advanced B-NHL

In the NHL-BFM-95 trial, when the dose of MTX was reduced for R1 and R2 patients, outcome was not inferior; however, reducing the infusion time of MTX from 24 hours to 4 hours for R3 and R4 group patients resulted in less mucositis, but inferior outcome.

EFS with best therapy in NHL-BFM-95 was more than 95% for R1 and R2 group patients and was 93% for R3 and R4 group patients. Inferior outcome was noted for patients with primary mediastinal B-cell lymphoma (50% 3-year EFS) and CNS disease at presentation (70% 3-year EFS). In the COG-C5961 (FAB/LMB-96) study, the outcome of group B patients, who had a greater than 20% response to cytoreductive prophase, was not affected by a reduction of the total dose of cyclophosphamide by 50% and elimination of one cycle of maintenance therapy. The 3-year EFS was 98% for stage I/II, 90% for stage III, and 86% for stage IV (CNS-negative) patients, while patients with primary mediastinal B-cell lymphoma had a 3-year EFS of 70%. In group C patients, reduction in cumulative dose of therapy and number of maintenance cycles resulted in inferior outcome. Patients with leukemic disease only, and no CNS disease, had 3-year EFS of 90%, while patients with CNS disease at presentation had a 70% 3-year EFS. This study identified response to prophase reduction as the most significant prognostic factor, with poor responders (i.e., < 20% resolution of disease) having an EFS of 30%. Both the BFM and FAB/LMB studies demonstrated that omission of craniospinal irradiation, even in patients presenting with CNS disease, does not affect outcome (COG-C5961 [FAB/LMB-96] and NHL-BFM-90).

Rituximab, a mouse/human chimeric monoclonal antibody targeting the CD20 antigen, has shown good responses in relapsed B-NHL and a promising response rate of more than 40% in a phase II study in newly diagnosed B-Cell NHL and BL. Based on results of a COG pilot study (ANHL01P1) that it is feasible and safe to include rituximab in the current chemotherapy backbone, an international study is evaluating the benefit of combining rituximab with standard chemotherapy in high-risk B-NHL patients, which currently remains to be proven.

Treatment of Anaplastic Large Cell Lymphoma

There is no consensus on management of ALCL due to the small number of patients treated in various studies; however the following broad principles can be derived.

Localized ALCL

Children with standard risk disease (Stage I/II completely resected with no high risk features such as involvement of skin, mediastinum, viscera, CNS or bone marrow) can be managed with three cycles (10–12 weeks) of B-cell type regimen and intrathecal therapy, to achieve an EFS of 90% as demonstrated by BFM, POG and ALCL-99 trials.

Disseminated ALCL

Children with disseminated ALCL have 5-year EFS of approximately 65–75%. The majority of European studies (BFM, SFOP, UKCCSG, ALCL-99) have used short duration (around 6 months) pulse intensive B-cell type approach with good results while American (COG) and Italian groups (AIEOP) have used longer duration (> 12 months) less intensive approach with almost equivalent survival but increased hematological toxicity.

BFM group used six cycles of intensive pulsed therapy, similar to their B-cell NHL therapy (NHL-BFM-90). A successor study found MTX 1 g/m^2 infused over 24 hours plus intrathecal MTX and MTX 3 g/m^2 infused over 3 hours without intrathecal MTX yielded similar outcomes, with less toxicity for the latter. Patients receiving an additional 1 year vinblastine exposure had a better EFS in the first year after therapy (91%) than those not receiving vinblastine (74%). However, after 2 years of follow-up, the EFS was 73% for both groups. The POG trial (POG-9317) demonstrated no benefit of adding methotrexate and high-dose cytarabine to 52 weeks of

a straightforward APO (doxorubicin, prednisone, and vincristine) regimen.

Patients with recurrent disease may obtain prolonged remission following the administration of single agent vinblastine. Two targeted therapies, brentuximab (anti-CD-30), and crizotinib (ALK tyrosine kinase inhibitor) have demonstrated significant initial activity in relapsed ALCL, but neither has been tested in a front-line protocol for newly diagnosed pediatric ALCL.

MORE ON THIS TOPIC

Attias, D, Hodgson D, Weitzman, S. Primary mediastinal B-cell lymphoma in the pediatric patient: can a rational approach to therapy be based on adult studies? Pediatric Blood Cancer. 2009;52:566-70.

D'souza MM, Jaimini A, Bansal A, et al. FDG-PET/CT in lymphoma. Indian J Radiol Imag. 2013;23:354-7.

Iyer VK. Pediatric lymphoma diagnosis: role of FNAC, biopsy, immunohisto-chemistry and molecular diagnostics. Indian J Pediatr. 2013;80: 756-63.

Laver JH, Kraveka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. J Clin Oncol. 2005;23:541-7.

Le Deley MC, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. J Clin Oncol. 2010;28:3987-93.

Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. The Lancet. 2012; 379:1234-44.

Naresh KN, Agarwal B, Nathwani BN, et al. Use of the World Health Organization (WHO) classification of non-Hodgkin's lymphoma in Mumbai, India: a review of 200 consecutive cases by a panel of five expert hematopatho-logists. Leuk Lymphoma. 2004;45:1569-77.

Reiter A. Diagnosis and treatment of childhood non-Hodgkin lymphoma. Hematology Am Soc Hematol Educ Programs. 2007;285-96.

Reiter A, Klapper W. Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. Br J Haematol. 2008;142:329-47.

Seidemann K, Tiemann M, Schrappe M, et al. Short-pulse B-non-Hodgkin lymphoma type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood. 2001;97:3699-706.

IN A NUTSHELL

1. Pediatric non-Hodgkin lymphomas (NHL) are diverse malignant lymphoid neoplasms derived from B or T, precursor or mature cells, most of which are high grade unlike NHL in adults.
2. Signs and symptoms of NHL depend on the type, site and extent of involvement of lymphoma and often occur over a few weeks owing to the rapid growth of tumor.
3. NHL commonly presents as enlarging, non-tender lymph-adenopathy, or with symptoms due to the compression of surrounding structures, such as wheezing, facial swelling or acute abdominal pain.
4. Potentially life-threatening complications of NHL need to be considered during the initial work-up and evaluation.
5. Adequate tissue should be obtained and reviewed by an experienced hematopathologist. If the patient is not stable, bone marrow, pleural effusion or other diagnostic sources can be considered.
6. Combination chemotherapy is the primary modality used for the treatment of pediatric NHL, with surgery and radiotherapy at a center experienced in the care of childhood cancer.
7. Modern chemotherapy protocols can cure 80–85% of pediatric NHL patients, but survival rates in India are lower due to delayed diagnosis, poor supportive care and abandonment.
8. Lymphoblastic lymphomas (T-cell and precursor B-cell) are treated with prolonged acute lymphoblastic leukemia like chemotherapy regimens whereas mature B-cell lymphomas are treated with brief, intensive chemotherapy regimens.
9. The value of additional agents such as nelarabine or rituximab is still being studied.
10. ALCL may be treated with chemotherapy similar to that used for mature B-cell lymphomas or a 1 year course of vincristine, doxorubicin and steroid with equivalent results.
11. Survivors of pediatric NHL are at increased risk for long-term sequelae, such as sterility, cardiomyopathy, and secondary malignancies due to the intensive chemotherapy used.
12. Positron emission tomography (PET) scan is helpful, but not essential, for the staging and management of pediatric NHL.

Chapter 45.8
Neuroblastoma
Maya Prasad, PA Kurkure

Neuroblastoma is an embryonal tumor derived from the sympathetic nervous system. It originates from the neural crest cells of the sympathetic nervous system and may arise from a number of widely separated anatomical sites along the craniospinal axis. Sites of primary tumor include cervical, cervicothoracic, thoracic, thoracoabdominal, abdominal, and pelvis.

It is the most common intra-abdominal solid tumor in childhood accounting for 8–10% of all pediatric cancers. Neuroblastoma is predominantly a disease of early childhood with approximately 85% of patients presenting before 6 years of age and 50% within the first 2 years of life, and it is the most common cancer diagnosed during infancy. It is seen only rarely in adults. Approximately, 50% of patients have disseminated disease at diagnosis. Neuroblastoma is one of the most fascinating tumors; the manifestations (detailed later) and natural history are diverse. Certain types of neuroblastoma, particularly in infants, may undergo spontaneous regression or may mature into a benign ganglioneuroma, whereas certain *high-risk* neuroblastomas tend to be aggressive and progress relentlessly.

EPIDEMIOLOGY

Neuroblastoma accounts for 8–10% of all childhood cancers in the developed world. There are between 650 and 800 new cases of neuroblastoma diagnosed per year in the United States, where the tumor has been found to be slightly more common in boys than in girls. In India, a recent epidemiological study showed that neuroblastoma accounted for between 2% and 3.8% of all cancers in children less than 14 years of age, making neuroblastoma less frequently reported than in the Western world. The male:female ratio ranges between 0.27 and 1.81, depending on the population sampled.

ETIOLOGY

As with most other pediatric embryonal tumors, the etiology of neuroblastoma is unknown. Although there have been anecdotal reports of parental environmental exposures leading to neuroblastoma, the data remains inconclusive. Very rarely, neuroblastoma may be familial exhibiting an autosomal dominant inheritance. Around 1–2% of cases of neuroblastoma have been associated with a mutation in the *ALK* gene. Neuroblastoma may also be seen in children with Hirschsprung disease and congenital central hypoventilation syndrome; these are associated with loss of function mutations in homeobox gene *PHOX2B*. Some cases have also been coincidentally observed in patients with disorders such as neurofibromatosis, Beckwith-Wiedmann syndrome and fetal hydantoin syndrome. However, no specific condition has been definitely linked to this tumor.

PATHOGENESIS

During the 5th week of embryogenesis, primitive sympathetic neuroblasts migrate from the neural-crest along the entire sympathetic chain. Neuroblastoma originates from these primitive cells; therefore, neuroblastoma can arise anywhere along the sympathetic nervous system. There are two clinically relevant aspects regarding the pathophysiology of neuroblastoma. Elevated metabolic byproducts of catecholamines—DOPA, dopamine, norepinephrine, and epinephrine—can be transiently detected in the urine of patients with neuroblastoma and other tumors of neural crest origin. DOPA and dopamine are metabolized into their final product, homovanillic acid (HVA), while norepinephrine and epinephrine are metabolized into vanillylmandelic acid (VMA), both of which are detected in the urine. Approximately, 90% of neuroblastoma tumors secrete these byproducts. The quantitative levels of urinary catecholamines—mainly urinary VMA and HVA—are useful not only in diagnosis, but also in evaluating response to treatment and during follow-up evaluation. Because neuroblastoma arises from the developing sympathetic nervous system, the majority of tumors express norepinephrine receptors on their cell surface. Metaiodobenzylguanidine (MIBG) is a norepinephrine analog; radiolabeled MIBG has been used to localize tumors which express norepinephrine receptors (such as neuroblastoma and pheochromocytoma), and also for targeted treatment in patients with MIBG avid tumors.

BIOLOGY

Some of the important biomarkers implicated in the pathogenesis of neuroblastoma are discussed as follows:

- *Amplification of MYCN Locus at 2p24 (more than 10 copies)* This occurs in approximately 30% of neuroblastoma and is associated with advanced disease at diagnosis, aggressive and rapid tumor progression and is an independent predictor of poor outcome. Even tumors with favorable features such as in infants and in loco regional disease are upstaged to *high risk* by the presence of *NMYC* amplification.
- *Unbalanced gain of 17q and deletion of 1 p* have also been clearly associated with more aggressive neuroblastomas, and advanced stage of disease. This has been attributed to the overexpression of survivin, an inhibitor of apoptosis.
- *Allelic loss of 11q* also has been recently found to be an independent predictor of disease relapse.
- *TrkA expression* Three tyrosine kinase receptors for a homologous family (Trk) of neurotrophin factors have been cloned. High levels of TrkA expression are highly correlated with favorable outcome, whereas expression of TrkB is strongly associated with aggressive tumor behavior and *MYCN*-amplification.
- *Tumor ploidy* Tumors that have a hyperdiploid DNA content (DI > 1) are more likely to have lower stages of disease and to respond to therapy.

Genetic Subsets

Relapsed neuroblastomas have been found to have an increased frequency of *TP53* gene mutations than primary tumors; however the significance is not clear. Based on the above biomarkers, neuroblastomas have been categorized into the following three distinct genetic subsets which have been found to have distinct behavior:

Type 1 Characterized by gains and losses of whole chromosomes; the karyotype is hyperdiploid or near triploid. There are no specific genetic changes, but these tumors express high levels of the TrkA neurotrophin receptor. These tumors are seen in infants and have a good prognosis; tumors may undergo spontaneous differentiation or regression.

Type 2A Characterized by gross chromosomal aberrations and copy number alterations. Apart from expression of the TrkB neurotrophin receptor, there are specific changes such as gain of 17q and loss of heterozygosity of 14q or 11q. These tumors lack

amplification of *MYCN* gene, but present with advanced stage disease and have a poor prognosis.

Type 2B These tumors have amplified *MYCN* gene as well as a gain of 17q, loss of 1p, and expression of the TrkB neurotrophin receptor. This is the most aggressive biological subtype with advanced stage at presentation and a rapid, relentless progression.

Familial neuroblastomas may be associated with mutations of *ALK* and *PHOX2B*; other recurrent gene mutations in patients with neuroblastoma include *PTPN11*, *ATRX* and *NRAS* (0.8%).

PATHOLOGICAL CHARACTERISTICS

Biopsy from a tumor suspected to be neuroblastoma is important not only for diagnosis, but also for staging using pathological classification systems as well as the study of biological markers which can be used for risk stratification. Histopathological characteristics of neuroblastoma are generally defined on tumor tissue prior to receiving chemotherapy; tumors undergo differentiation after treatment, and this may confound pathological examination.

Based on the degree of differentiation, neuroblastoma can be classified into three histological subgroups: (1) neuroblastoma, (2) ganglioneuroblastoma, and (3) ganglioneuroma. Neuroblastoma is the most primitive entity—it consists of dense nests of cells separated by fibrillary bundles and frequently demonstrates hemorrhage, necrosis and calcification. A characteristic finding is the presence of rosettes in which tumor cells surround a pink fibrillar center (Homer Wright pseudorosettes). By contrast benign ganglioneuroma consists of mature ganglion cells, embedded in a bulky stroma composed of Schwann cells and nerve bundles. Between these two extremes is the transitional form known as ganglioneuroblastoma. The three classic histopathologic patterns of neuroblastoma, ganglioneuroblastoma, and ganglioneuroma reflect a spectrum of maturation and differentiation (**Fig. 1**). There are two commonly used histopathological classification systems: (1) Shimada histology classification utilizes patient age and the presence or absence of Schwannian stroma, the degree of differentiation, and the Mitosis-Karyorrhexis Index (MKI), to assign tumors to a favorable or unfavorable category. (2) More recent studies have used the International Neuroblastoma Pathology Classification (INPC), which is a modification of the Shimada system and places pretreatment tumors into two broad categories of *favorable* and *unfavorable* histology based on amount of Schwannian stromal component, degree of differentiation, MKI, and patient age.

Neuroblastoma is one of several small blue round cell tumors (SBRCTs) of childhood and it may be difficult to differentiate from lymphoma, Ewings sarcoma—primitive neuroectodermal tumors, and rhabdomyosarcoma by light microscopy alone. The definitive diagnosis is commonly made by immunohistochemistry as well as supporting clinical features and ancillary investigations. On immunohistochemical staining, neuroblastomas are positive for neurofilament proteins, chromogranin, synaptophysin, and neuron specific enolase (NSE) (**Table 1**).

CLINICAL FEATURES

Physical examination of a child with neuroblastoma should include detailed evaluation of the primary mass as well as draining lymph node structures. General examination could reveal proptosis, Horners syndrome, or lytic skull lesions. Detailed neurologic examination of a patient with spinal lesion may detect impending neurological compromise. The manifestations of neuroblastoma are varied, and can be broadly divided as following:

Manifestations due to Primary Tumor

Since neuroblastoma originates from the neural crest cells of the sympathetic nervous system, they may arise from a number of widely separated anatomical sites along the craniospinal axis. The most frequent anatomical sites of primary tumors are the adrenal gland (32%), paravertebral retroperitoneum (28%), posterior mediastinum (15%), pelvis (5%) and cervical area. Abdominal tumor may present as a mass which is usually firm and irregular and often crosses the midline (**Fig. 2**). The mass may cause compression of neighboring abdominal structures and lead to complications such as hydronephrosis and bowel obstruction. Tumors with intraspinal extension or spinal cord compression lead to neurological symptoms such as flaccid paralysis of the legs and/or bladder or bowel dysfunction. Cervical masses from primary or metastatic neuroblastoma may cause Horner syndrome, which consists of unilateral ptosis, miosis and anhydrosis. Occasionally, large thoracic tumors are associated with mechanical obstruction and occasionally result in superior vena cava syndrome.

Symptoms due to Metastatic Spread

The tumor spreads through the lymphatics and blood. Sites of metastases include the distant lymph nodes, bone, bone marrow, liver, skin, brain, spinal cord and very rarely lungs. Characteristic descriptions of metastatic neuroblastoma are *raccoon eyes* due
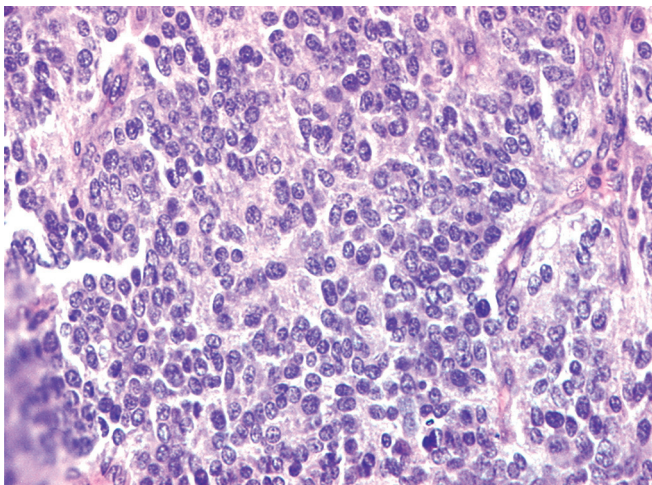
Figure 1 Microscopy (hematoxylin and eosin [H/E] staining) of neuroblastoma, which is seen as a small round blue cell tumor

Table 1 Immunohistochemical features of pediatric small round cell tumors which can present as abdominal mass

Tumor	Immunohistochemical markers
Neuroblastoma	Neuron-specific enolase, chromogranin, synaptophysin, TrkA, ganglioside (GD2)
Rhabdomyosarcoma	Myogenin, desmin, muscle-specific actin, vimentin, MyoD1
Ewing sarcoma/primitive neuroectodermal tumors (PNET)	CD99, β2-microglobulin, synaptophysin, vimentin
Lymphoma	CD45, CD3, CD5, CD7, CD19, CD20
Synovial sarcoma	Epithelial membrane antigen (EMA), cytokeratin, Bcl-2, TLE-1
Desmoplastic small round cell tumors (DSRCT)	Desmin, cytokeratin, WT-1, EMA, CD57

Figure 2 Infant with neuroblastoma presenting with gross abdominal distension and *pepper liver*

to periorbital edema and ecchymosis (**Fig. 3**), *pepper liver* due to liver involvement and subcutaneous nodules (blueberry muffin syndrome). Persistent anemia and thrombocytopenia due to bone marrow infiltration may also be a presentation.

Paraneoplastic Phenomena

Neuroblastoma can unusually present with *paraneoplastic pheno-mena*. Opsoclonus myoclonus syndrome (OMS) consists of rapid eye movements, ataxia, and myoclonus, and is observed in 2–4% of newly diagnosed neuroblastoma patients. Most children with this syndrome have a favorable outcome with respect to their tumor; this may correlate with immune-mediated antitumor host response. However, the neurologic and cognitive deficits may persist in the long-term. The vasoactive intestinal peptide (VIP) syndrome associated with diarrhea, hypokalemia and dehydration is a manifestation of tumor secretion of VIP. Systemic features such as fever, sweating, hypertension, and anemia are often manifestations of catecholamine release.

Infants (less than 18 months of age) with stage 4S disease have a favorable subtype of disease. They usually present with a localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver and/or bone marrow (less than 10%). These tumors tend to regress spontaneously, but may require treatment if symptomatic, e.g., rapidly enlarging liver or respiratory embarrassment.
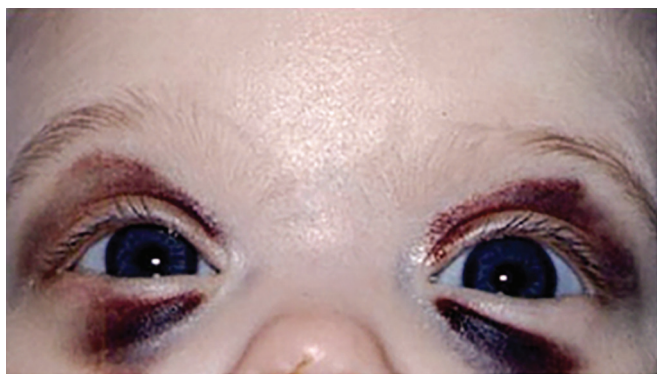
Figure 3 Child with metastatic neuroblastoma presenting with *raccoon eyes*

DIFFERENTIAL DIAGNOSES

Several conditions can be confused with neuroblastoma due to the wide range of clinical manifestations. In a young child with a large abdominal mass, the differentials include other neoplasms such as Wilms tumor and hepatoblastoma. Children with disseminated bone disease may mimic acute leukemia or infectious/inflammatory diseases. Other metastatic sites like cranial bones/paraspinal soft tissue may mimic primary tumors arising from those areas. Histologically, neuroblastoma needs to be distinguished by immunohistochemistry (IHC) from other small, round blue-cell tumors such as rhabdomyosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET), lymphoma, and leukemia. The distinguishing features on IHC are detailed in **Table 1**.

APPROACH TO DIAGNOSIS

A detailed physical examination, including neurologic examina-tion is essential in the evaluation of a child suspected to have neuroblastoma.

Diagnostic Criteria

The international criteria for diagnosis of neuroblastoma, state that diagnosis must be based on one of the following: (1) an unequivocal pathologic diagnosis made from tumor tissue by light microscopy (with or without IHC, or increased levels of serum catecholamines or urinary catecholamine metabolites [VMA or HVA]); or (2) the combination of bone marrow aspirate or trephine biopsy containing unequivocal tumor cells (e.g., syncytia or immunocytologically-positive clumps of cells) and increased levels of serum catecholamines or urinary catecholamine metabolites.

Initial Evaluation

As with all other childhood malignancies, initial evaluation includes complete blood count, liver and kidney function tests. The goal of diagnostic testing is to definitively establish the diagnosis and precisely define the disease burden. Specific diagnostic work-up of neuroblastoma includes biopsy from tumor for pathological examination (including IHC) and *MYCN* gene amplification studies (usually by fluorescent in situ hybridization [FISH]/quantitative polymerase chain reaction [PCR]). Levels of urinary catecholamine metabolites HVA and VMA are commonly measured for diagnostic purposes and to follow response to therapy.

Ideally, imaging of the primary tumor should be done by either computed tomography (CT) scan or magnetic resonance imaging (MRI) of local region, depending upon the site. In practice, CT scan of thorax/abdomen and pelvis will be useful in most cases of neuroblastoma, while tumors of head and neck or spine require MRI (**Figs 4 to 6**). Essential staging/metastatic work-up consists of bilateral bone marrow biopsies and imaging studies, preferably MIBG scan, which is applicable to all sites of disease (primary as well as metastatic sites). MIBG scan using either ^{123}I-MIBG or ^{131}I-MIBG radionucleotide is a highly sensitive and specific imaging modality, and is now considered an essential part of staging work-up as well as response evaluation in neuroblastoma (**Fig. 7**). Positron emission tomography (PET)-CT is gaining acceptance in the staging workup of neuroblastoma. [99]Technetium bone scan is an alternative for bony lesions if MIBG scan is unavailable.

STAGING OF NEUROBLASTOMA

Staging of neuroblastoma has evolved with advances in the understanding of disease biology. The classic staging system

Figure 4 Computed tomography (CT) scan of large abdominal neuroblastoma with minimal calcification
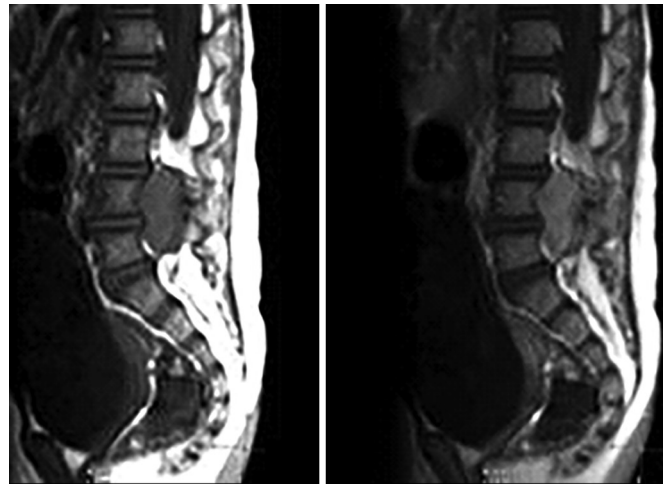
Figure 6 Magnetic resonance imaging (MRI) of dorsolumbar spine showing neuroblastoma with intraspinal extension

Figure 5 Computed tomography (CT) scan of thorax showing mediastinal neuroblastoma
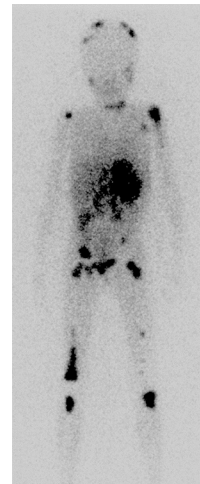
Figure 7 Metaiodobenzylguanidine (MIBG) scan of a child with adrenal primary neuroblastoma and extensive skeletal metastasis

proposed by Evans gave way to the International Neuroblastoma Staging System (INSS) (**Table 2**), a postoperative staging system which is commonly used now.

PROGNOSTIC FACTORS

Several prognostic factors have been identified in neuroblastoma—the most consistent being age at diagnosis, stage at presentation and *N-myc* amplification.

Age at Diagnosis
Although earlier studies had found that children less than 1 year at diagnosis had a better outcome, recent evidence shows that 18 months is a more clear cutoff of outcome.

Stage
Stage of disease by the INSS is clearly correlated with patient outcome (higher stages have poorer outcome) and is used by all cooperative groups to stratify therapy.

N-myc Amplification
It is also a powerful, independent adverse prognostic marker. Other markers such as tumor ploidy, deletion of chromosome 1p, and

gain of chromosome 17q are found to confer an adverse prognosis. Several other biological markers such as cell telomere length, telomerase activity, *TrkA* gene expression, serum neuron-specific enolase level, etc., have been found important in prognosis, but are not routinely used.

Tumor Pathology
The International Neuroblastoma Pathology Classification (INPC) places pretreatment tumors into two broad categories of *favorable* and *unfavorable* histology based on amount of Schwannian stromal component, degree of differentiation, MKI, and patient age.

Risk Stratification
This is ideally done by a multidisciplinary team at a tertiary center with advanced radiology and pathology facilities. Risk stratification in neuroblastoma is based on variables such as age, clinical stage, histopathology and biology.

International Neuroblastoma Risk Group Staging System
The International Neuroblastoma Risk Group Staging System (INRGSS) is the latest staging system for neuroblastoma—a preoperative staging, in which the extent of disease is determined

Table 2 International neuroblastoma staging system (INSS)

Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver and/or bone marrow (limited to infants < 1 year of age).

by the presence or absence of image-defined risk factors (IDRFs) and/or metastatic tumor at the time of diagnosis, before any treatment. This staging system also takes into account the molecular biology of disease (DNA ploidy, *MYCN* amplification status and 11q), apart from the conventional factors such as age, stage and grade of tumor differentiation. Tumors are classified into 16 statistically distinct groups, under four broad categories: (1) Very low, (2) Low, (3) Intermediate and (4) High risk. This system is yet to undergo prospective international validation.

TREATMENT

Surgery, radiation therapy and chemotherapy are all used in the treatment of neuroblastoma (**Table 3**). Treatment of neuroblastoma should be tailored to the risk category, and may vary widely from cautious observation alone to aggressive multimodal treatment.

Surgery

Surgery plays a pivotal role in the management of neuroblastoma, both for diagnosis and for treatment. Apart from helping to establish the diagnosis, the postoperative specimen also provides tissue for genetic studies. Although excision of tumor is essential, a maximal safe resection (rather than a radical surgery) is often considered adequate. Delayed surgery after chemotherapy is performed with a low rate of complications, achieving a good local control of disease.

Chemotherapy

Chemotherapy is the predominant modality of management in neuroblastoma, which is an exquisitely chemosensitive disease. The drugs commonly used include a combination of cyclophosphamide, cisplatin, doxorubicin, and etoposide. Other drugs such as ifosfamide, carboplatin and topotecan/irinotecan are also used as second-line agents.

Radiotherapy

Radiation therapy is an essential part of management of high-risk neuroblastoma for local control of primary tumor as well as for control of metastatic sites. It may also be useful in low- or intermediate-risk neuroblastoma with symptomatic life-threatening or organ-threatening tumor bulk that does not respond rapidly enough to chemotherapy. Radiation is also a means of symptom control (palliation) painful end-stage disease, and may be combined with MIBG as a targeted therapy.

Risk Stratified Therapy

Low-Risk Disease

In patients with low-risk disease, surgery alone is adequate. In certain situations, a combination of surgery and chemotherapy is used (e.g., spinal cord compression, respiratory compromise secondary to hepatic infiltration). Some groups have reported observation alone without surgery for localized, suspected adrenal neuroblastoma in infants. Low-risk neuroblastoma has a cure rate higher than 90% in most studies.

Treatment of Stage 4S Neuroblastoma

Most patients in this subgroup are classified as low-risk and can be managed by observation alone, as these tumors tend to

Table 3 Risk adapted approach to treatment of neuroblastoma

Risk category	Stage	Age (months)	N-myc	INPC classification	Treatment	Survival
Low	1 2A/2B	Any	Non-Amp	Any	Surgery ± Low dose chemotherapy	90%
	4S (Very low risk)	< 12	Non-Amp		*Asymptomatic:* Observation *Symptomatic:* Low dose chemotherapy/radiation	
Intermediate	3	< 18	Non-Amp	Any	Surgery + chemotherapy ± radiation	70–90%
		> 18	Non-Amp	Favorable		
	4	< 18	Not Amp	Any		
High	3	> 18	Non-Amp	Unfavorable	*Induction:* Multiagent chemotherapy *Local treatment:* Surgery + radiation	30–40%
	4	> 18	Any		Consolidation with myeloablative chemotherapy and autologous stem cell transplant	
	Any	Any	Amp		Differentiation therapy with 13-cis-retinoic acid ± immunotherapy	

Abbreviations: INPC, international neuroblastoma pathology classification; Amp, amplified.

regress spontaneously. Asymptomatic infants with 4S disease have been reported to have 100% survival with supportive care only. Symptomatic patients (huge hepatomegaly, respiratory or impending neurological compromise) benefit from short courses of low dose chemotherapy.

Intermediate-Risk Neuroblastoma

Patients with intermediate-risk neuroblastoma require a combination of surgery and chemotherapy (4–8 cycles of multi-agent chemotherapy). According to Western literature, infants aged 1 year and younger have a greater than 80% cure rate while older children have a cure rate of 50–70%.

High-Risk Neuroblastoma

The treatment of high-risk neuroblastoma remains a challenge world-over with outcomes of 30–50% even at the best centers. The intensive multimodality approach consists of (1) induction chemotherapy, followed by (2) consolidation with surgery, stem cell transplant, radiation therapy and (3) treatment of minimal residual disease using differentiating agents and/or immunotherapy.

Induction therapy consists of multiagent chemotherapy (combinations of cyclophosphamide, ifosfamide, cisplatin, carboplatin, vincristine, doxorubicin, etoposide and topotecan).

Local control Surgical resection of primary tumor site is done after induction chemotherapy. Even patients with stage 4 disease older than 18 months benefit from gross-total resection of the primary tumor mass after chemotherapy. All patients with high-risk neuroblastoma need to undergo radiation to primary tumor site. Myeloablative consolidation therapy, as well as control of minimal residual disease using differentiation agents such as 13-*cis*-retinoic acid has also been shown to improve survival significantly. Immunotherapy using anti-GD2 (gangliosidase) antibodies are also being incorporated into standard treatment protocols. Despite this aggressive approach, outcomes in high-risk neuroblastoma remain dismal; long-term survival with current treatments is about 30–50% even in the best of centers. This has led to continued efforts to improve outcomes using other experimental therapies such as aurora kinase inhibitors, antiangiogenic agents, histone deacetylase inhibitors, and MIBG therapy. [131]I MIBG therapy is being used with increased frequency in upfront treatment as well as in relapsed neuroblastoma.

OUTCOMES

Western data shows a uniformly excellent prognosis (> 90%) for low-risk neuroblastoma; some studies show more than 95% survival. Patients with intermediate-risk neuroblastoma also do well, with 80–90% cure rates. However, even at the best centers, patients with high-risk neuroblastoma do poorly with approximately 40–50% survival rates. Asymptomatic patients with stage 4S disease have nearly 100% survival.

There is data from several centers in India, which includes approximately 700 patients. The reported survival outcome ranges between 8.7% and 80% at different centers; poor outcomes are likely due to high mortality and relapse/progression along with treatment abandonment. Hopefully, improvement in diagnostic and treatment infrastructure as well as financial and social support (to prevent treatment refusal and abandonment) will see an improvement in outcomes across India.

Late Effects of Treatment

Late effects of treatment are seen mostly in high-risk patients. Side effects of chemotherapy include sensorineural hearing loss (cisplatin/carboplatin), cardiotoxicity (anthracyclines), sterility and second malignancies (alkylating agents and topoisomerase II inhibitors). Depending on the site of original tumor, patients may have organ dysfunction resulting from local radiation and surgery. Especially of concern is the fact that neuroblastoma is a disease of young children, who are at a higher risk of developing complications. Children who present with OMS may have chronic neurologic disability and cognitive deficits, even though the primary tumors respond well to treatment. These children might benefit from targeted immunomodulating therapy in the acute phase; early identification of affected children enables follow-up and neurological/cognitive rehabilitation.

FUTURE DIRECTIONS

Neuroblastoma remains the most fascinating pediatric tumor. Outcomes in low- and intermediate-risk neuroblastoma are good with existing treatment protocols. However, the treatment of high-risk neuroblastoma remains a challenge in the best of centers. Several newer therapeutic options are being studied. It is hoped that further understanding of the molecular and genetic biology of this disease will lead to improved prognostication and subsequently more effective and less toxic therapy.

MORE ON THIS TOPIC

Arora RS, Eden TOB, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer. 2009;46:265-73.

Brodeur GM, Hogarty MD, Mosse YP, Harris JM. Neuroblastoma. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2011. pp. 886-922.

Cheung NK, Dyer MA Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer. 2013;13:397-411.

Kulkarni KP, Marwaha RK. Outcome of neuroblastoma in India. Indian J Pediatr. 2013;80:832-7.

Maris JM. Recent advances in neuroblastoma. N Engl J Med. 2010;362:2202-11.

Matthay KK, George RE, Yu AL. Promising therapeutic targets in neuroblastoma. Clin Cancer Res. 2012;18:2740-53.

Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Eng J Med. 1999;341:1165-73.

Modak S, Cheung NK. Neuroblastoma: therapeutic strategies for a clinical enigma. Cancer Treat Rev. 2010;36:307-17.

Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010;363: 1324-34.

IN A NUTSHELL

1. Neuroblastoma is the most common intra-abdominal solid tumor in childhood accounting for 8–10% of all pediatric cancers in the West (2–3.8% in India).
2. 85% of patients present before 6 years of age.
3. Neuroblastoma, particularly in infants, is well known to undergo spontaneous regression and maturation.
4. Amplified *N-myc* (more than 10 copies)—occurs in approximately 30% of neuroblastoma and is associated with advanced disease at diagnosis and poor outcome.
5. Outcome in low- and most intermediate-risk neuroblastoma is excellent; however, the treatment of high-risk neuroblastoma remains extremely challenging.
6. Advances in research are leading to an improved understanding of the biology of neuroblastoma and hence to refined risk stratification and novel, improved therapeutic approaches.

Chapter 45.9
Wilms Tumor
Sajid Qureshi, Monica Bhagat

Wilms tumor (WT) is the most common renal tumor in children. Treatment of WT has evolved from surgical excision alone to combined multimodal treatment over past few decades. Large randomized controlled trials by various collaborative groups, including the National Wilms Tumor Study Group (NWTSG), The International Society of Pediatric Oncology (SIOP) and the United Kingdom Children's Cancer Study Group (UKCCSG) have facilitated WT treatment to be customized to minimize morbidity for low-risk disease and to maximize the prognosis for high-risk patients. Consequently the outcome for patients with WT has improved remarkably. However, these success stories from the developed world are not directly translated in resource constrained countries. Over 80% of the world children have poorer chance of survival due to limited access to appropriate specialist care. Nonetheless, robust evidence generated through the cooperative studies should guide caregivers to utilize resource adapted therapy with better organization and coordination of existing services.

EPIDEMIOLOGY

Wilms tumor accounts for 6% of all pediatric malignancies. It predominantly affects children less than 5 years of age commonly during the first 2 years of life. Occasionally WT has also been described in teenagers and adults. Although the incidence of renal tumors in India is not well documented, the available information reveals an incidence range of 5–9 per million for males and 3–10 per million for females in children 0–14 years of age in selected geographical areas, which is nearly same as that reported from developed countries like USA and has remained stable for many years.

ETIOLOGY

Wilms tumor normally develops in otherwise healthy children; however, 10% of cases occur in individuals with recognizable phenotypic syndrome. The conditions in which there is an increased risk of WT are given in **Table 1**. Several epidemiological studies have investigated occupational, environmental, and lifestyle characteristics as potential risk factors for WT. A meta-analysis has identified significantly increased risk of WT with maternal exposure to pesticides prior to child's birth, high birthweight and preterm birth. Additionally, an increased though not statistically significant risk of WT was associated with maternal hypertension and compared with the first born, being a second or later birth was associated with a significantly decreased risk.

PATHOPHYSIOLOGY

Genetic and molecular studies have contributed important insights to understanding the pathogenesis of WT. The WT gene-1 (*WT1*) is a tumor suppressor gene located on the short arm of chromsome 11 (11p13). The normal function of *WT1* is required for normal genitourinary development and is important for differentiation of the renal blastema. The identification of this suppressor gene was made on cytogenetic analysis of patients with WAGR (Wilms tumor, Aniridia, Genitourinary tract abnormalities, mental Retardation) syndrome who have more than 30% risk of developing WT. A gene that causes aniridia (*PAX-6*) is located near the *WT1* gene

Table 1 Phenotypic syndromes and other conditions associated with increased risk of Wilms tumor

Risk	Syndrome
High risk (> 20%)	*WT1* associated (WAGR syndrome and Denys-Drash syndrome)
	Familial Wilms tumor
	Perlman syndrome
	Mosaic variegated aneuploidy
	Fanconi anemia D1/biallelic *BRCA2* mutations
Moderate risk (5–20%)	Frasier syndrome
	Beckwith-Wiedemann syndrome
	Simpson-Golabi-Behmel syndrome
Low risk (< 5%)	Isolated hemihypertrophy
	Bloom syndrome
	Li-Fraumeni syndrome-like syndrome
	Hereditary hyperparathyroidism-jaw tumor syndrome
	Mulibrey nanism
	Trisomy 18
	Trisomy 13
	2q37 deletions

Abbreviations: WT1, Wilms tumor gene 1; WAGR, Wilms tumor, Aniridia, Genitourinary tract abnormalities, mental retardation; BRCA, BReast CAncer gene 2

on chromosome 11p13, and deletions encompassing the *WT1* and aniridia genes explain the association between aniridia and WT. Denys-Drash syndrome, with 95% chance of development of WT, is another syndrome associated with *WT1* gene mutation. Although *WT1* has a clear role in tumorigenesis of WT in earlier patients, only a small number of patients with sporadic WT have *WT1* mutations suggesting that other genes are also involved in WT development. The other most often mutated genes identified in WT include *TP53*, *CTNNB1* (encoding β-catenin) and *WTX*.

CLINICAL FEATURES

There are no explicit clinical features of WT. Most commonly patients present with an abdominal mass accidentally noted by the parents or during routine clinical examination (**Fig. 1**). However, about one-third of patients present with abdominal pain, anorexia, vomiting, malaise, or a combination of these symptoms. Gross or microscopic hematuria is found in 30% of patients. Hypertension

Figure 1 Large renal mass crossing the midline

is present in about 25% and is attributed to increase in renin activity. Occasional presentation in a subset of patient is rapid enlargement of the abdomen associated with fever, anemia and hypertension as a result of sudden subcapsular hemorrhage. Features of congenital syndromes associated with WT like genitourinary malformation (hypospadias, cryptorchidism, etc.), aniridia, Beckwith-Wiedemann syndrome (BWS)-associated facial dysmorphism, hemihypertrophy, etc., may be present. In rare cases of renal vein or caval extension of tumor, varicocele, hepatomegaly, ascites or congestive heart failure may be present.

DIFFERENTIAL DIAGNOSES

Any renal mass may mimic WT since it has no characteristic clinicoradiological signs. The common malignant renal tumors include non-Wilms primary renal tumors (like rhabdoid tumors, primitive neuroectodermal tumors [PNET], etc.), leukemia and Burkitt lymphoma. Benign conditions that may mimic WT include polycystic kidney disease, abscess, and hydronephrosis. The primary extrarenal tumors that may be mistaken for WT include neuroblastoma and other retroperitoneal tumors.

APPROACH TO DIAGNOSIS

Laboratory Investigation

Conventional laboratory investigation including complete blood count, liver function tests, renal function including, electrolytes, and serum calcium are performed. Acquired von Willebrand disease can occur in approximately 1–2% of patients with WT, therefore coagulation profile should also be performed.

Imaging

The conventional imaging modality for WT has been a computed tomography (CT) scan, however most patients undergo an ultrasound examination as the initial radiographic study. A CT scan without observer variation gives an objective assessment of features of the renal mass, the extent, intravascular extension of tumor and the status and function of the contralateral kidney (**Fig. 2**). The evaluation of the lungs for metastases with chest X-ray alone or with CT scan and their subsequent management differs amongst the cooperative groups. Nevertheless, a CT scan of the chest gives a better assessment of the pulmonary metastasis. The value of magnetic resonance imaging (MRI) in WT is the higher resolution allowing the detection of smaller lesions as well as the minimization of ionizing radiation exposure in young children. The differentiation of nephrogenic rests from WT could also be made for diagnosis and planning of nephron-sparing surgery by different MRI modalities. The role of positron emission tomography (PET) scan is not well documented for WT, though some have considered it useful for relapsed patients. However, with limited availability and economic constrains in most developing countries routine use of PET scan should be restricted till further evidence become available.

Tissue Diagnosis

Achieving a diagnosis by means of biopsy at presentation, prior to initiation of therapy is contentious. The NWTSG forbids biopsy before surgery and upstage the disease if biopsy has been performed. On the contrary, the SIOP group initiates chemotherapy without a biopsy, in all patients with renal masses. The UKCCG did

Figures 2A to G (A) Well circumscribed right renal mass; (B) Perinephric spread (arrows); (C) Intra-atrial extension of Wilms tumor; (D) Bilateral Wilms tumor; (E) Extensive retroperitoneal lymphadenopathy; (F) Bilateral pulmonary metastases; (G) Liver metastases

not find any increased risk of recurrence or major complications with pretreatment biopsy rather 12% of patients were identified with non-WT who could receive therapy appropriate for their diagnosis. As a consequence to this the last SIOP 2001 study does not upstage the disease if biopsy is performed before therapy. In light of this difference of opinion, a balanced decision for biopsy should be taken considering operability and general condition of the patient.

Staging

Due to the different treatment schedule by the two large cooperative study groups two major staging systems are currently used: a forthright, surgery-based system developed by the NWTSG and a delayed surgery-based system developed by SIOP (**Tables 2 and 3**). Although a direct comparison is not practical due to the difference in surgical timing both staging systems are valuable in predicting outcomes.

Table 2 Staging system of the National Wilms Tumor Study (upfront surgery)

Stage I	Tumor limited to the kidney and completely excised
	(a) The renal capsule is intact
	(b) The tumor was not ruptured or biopsied prior to removal
	(c) The vessels of the renal sinus are not involved
	There is no evidence of tumor at or beyond the margins of resection
	Note: For a tumor to qualify as Stage I, regional lymph nodes must be examined microscopically
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection
	The tumor extends beyond kidney, as is evidenced by any one of the following criteria:
	(a) There is regional extension of the tumor (i.e., penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus
	(b) Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor
	Note: Rupture of spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III
Stage III	Residual nonhematogenous tumor present following surgery, and confined to abdomen
	Any one of the following may occur:
	(a) Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for stage IV),
	(b) The tumor has penetrated through the peritoneal surface,
	(c) Tumor implants are found on the peritoneal surface,
	(d) Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination),
	(e) The tumor is not completely resectable because of local infiltration into vital structures,
	(f) Tumor spillage occurring either before or during surgery,
	(g) The tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type-tru-cut, open or fine needle aspiration) before removal,
	(h) Tumor is removed in greater than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present)
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the earlier criteria on the basis of the extent of disease

Table 3 Staging system of International Society of Pediatric Oncology (SIOP) (upfront chemotherapy)

Stage I	(a) Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected (resection margins clear)
	(b) The tumor may be protruding into the pelvic system and dipping into the ureter (but it is not infiltrating their walls)
	(c) The vessels of the renal sinus are not involved
	(d) Intrarenal vessel involvement may be present
	FNAC or core needle biopsy does not upstage the tumor
	The presence of necrotic tumor or chemotherapy-induced changes in the renal sinus and/or within the perirenal fat should not be regarded as reason for upstaging a tumor providing it is completely excised and does not reach the resection margins
Stage II	(a) Tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins clear)
	(b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but it is completely resected
	(c) The tumor infiltrates adjacent organs or vena cava but is completely resected
Stage III	(a) Incomplete excision of the tumor which extends beyond resection margins (gross or microscopical tumor remains postoperatively)
	(b) Any abdominal lymph nodes are involved
	(c) Tumor rupture before or intraoperatively (irrespective of other criteria for staging)
	(d) The tumor has penetrated through the peritoneal surface
	(e) Tumor implants are found on the peritoneal surface
	(f) The tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon
	(g) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery
	The presence of necrotic tumor or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as proof of previous tumor with microscopic residue and therefore the tumor is assigned stage III
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
Stage V	Bilateral renal tumors at diagnosis. Each side should be substaged according to the above criteria

Abbreviation: FNAC, fine needle aspiration cytology.

Pathology

A classic WT is triphasic, with variable proportions of blastemal, stromal and epithelial components. Biphasic or monophasic patterns are also encountered. The pathology is perhaps the most powerful prognostic factor for WT and is utilized in treatment planning by both the NWTS and the SIOP groups. The NWTSG classifies WT based on the presence or absence of anaplasia into unfavorable (UH) and favorable histology (FH) respectively. The SIOP trials recognized three prognostic groups of WT based on the histologic features after chemotherapy: low-risk, intermediate-risk, and high-risk tumors (**Table 4**).

Nephrogenic Rest

Nephrogenic rest is defined as the persistence of metanephric tissue in the kidney after the 36th week of gestation. As they are found in 30–40% of the kidney removed for WT they may be considered as precursor of WT. Nephrogenic rests are subclassified by their position within the renal lobe (**Fig. 3**). Perilobar nephrogenic rests are limited to the periphery of the renal cortex and are usually multiple. They contain predominantly blastema and tubules and reflect later disturbances in nephrogenesis. The intralobar nephrogenic rests occur randomly deep within the renal lobe and are usually solitary. They contain predominantly stroma and reflect earlier disturbances in nephrogenesis. The presence of multiple nephrogenic rests is termed as nephroblastomatosis. Majority of the nephrogenic rest involute spontaneously, some may undergo hyperplastic overgrowth and only a small number develop clonal transformation into WT. Presence of nephrogenic rests within a kidney resected for a WT indicates the need for monitoring the contralateral kidney for tumor development, particularly in young infants.

MANAGEMENT

The histologic grade and stage of the tumor are the most important determinant of outcome in WT. An accurate intraoperative staging is required to assess the requirements for postoperative treatment with chemotherapy or radiotherapy. The chronology of delivery of multimodal treatment in SIOP and NWTS protocol is described in **Tables 5 and 6**.

Surgery

The timing of surgery with regards to preoperative therapy has varied between the European and North American group. Nevertheless, surgical resection is an important constituent in the multimodal management of WT. Debates about the exploration of contralateral kidney at surgery exist but evidence now suggests it can be omitted. Data from NWTS 4 study showed omission of routine exploration does not affect the outcome or management of newly diagnosed WT, if adequate preoperative CT or MRI is obtained. A transperitoneal approach is preferred to provide

Table 4 International Society of Pediatric Oncology (SIOP) working classification of renal tumors of childhood (2001)

Pretreated cases	Primary nephrectomy cases
I. *Low-risk tumors*	I. *Low-risk tumors*
Mesoblastic nephroma	Mesoblastic nephroma
Cystic partially differentiated nephroblastoma	Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma	
II. *Intermediate-risk tumors*	II. *Intermediate-risk tumors*
Nephroblastoma—epithelial type	Nonanaplastic nephroblastoma and its variants
Nephroblastoma—stromal type	
Nephroblastoma—mixed type	Nephroblastoma—focal anaplasia
Nephroblastoma—regressive type	
Nephroblastoma—focal anaplasia	
III. *High-risk tumors*	III. *High-risk tumors*
Nephroblastoma-blastemal type	Nephroblastoma—diffuse anaplasia
Nephroblastoma-diffuse anaplasia	Clear cell sarcoma of the kidney
Clear cell sarcoma of the kidney	Rhabdoid tumor of the kidney
Rhabdoid tumor of the kidney	

Figure 3 Nephroblastomatosis

Table 5 Treatment regimens for Wilms tumor (WT) from International Society of Pediatric Oncology (SIOP) studies

Stage	Preoperative	Postoperative	Radiation therapy
I	VA × 4 weeks	VA × 4 weeks	
II	VA × 4 weeks	VDA × 27 weeks	Node-positive: 15 Gy
III	VA × 4 weeks	VDA × 27 weeks	15 Gy
IV	VDA × 6 weeks	CR after 9 weeks: VDA × 27 weeks	None if lung lesions disappear by week
		No CR after 9 weeks: ICDE × 34 weeks	

Abbreviations: V, vincristine; A, actinomycin-D; D, doxorubicin; I, ifosfamide; C, carboplatin; E, etoposide.

Table 6 Treatment regimens for Wilms tumor from National Wilms Tumor studies (NWTS)

Stage	Chemotherapy	Radiation therapy
I FH/UH and II FH	VA × 18 weeks	Nil
III FH	VDA × 24 weeks	10.8 Gy
IV FH	VDA × 24 weeks	10.8 Gy flank (if local stage III) 12 Gy lung (if lung metastasis)
II–IV UH	VCDE × 24 weeks	10.8 Gy flank (if local stage III) 12 Gy lung (if lung metastasis)

Abbreviations: V, vincristine; A, actinomycin-D; D, doxorubicin; C, carboplatin; E, etoposide; UH, unfavorable histology; FH, favorable histology.

adequate exposure for complete staging, which includes inspection for local tumor extension, hilar and regional lymph nodes, liver metastases and peritoneal seedlings. Prevention of tumor spillage should be of prime concern as this has a bearing in upstaging the tumor, hence gentle handling and careful removal is mandatory. The inferior vena cava (IVC) and the renal vein should be palpated for the presence of tumor thrombus, which if present should be removed en-bloc along with the kidney (**Fig. 4**). Generally, WT does not infiltrate the adjoining structures; hence, a radical en-bloc resection is rarely needed. The presence or absence of disease in hilar and regional lymph nodes is an extremely important factor in accurate staging and therefore appropriate treatment. Routine lymph node sampling from the renal hilum and the paracaval or para-aortic areas must be performed; however a formal lymph node dissection is avoided.

Partial nephrectomy in the routine management of WT has not gained popularity. The reasons being most WT are large or centrally located making only less than 5% eligible for partial nephrectomy at presentation and even after preoperative chemotherapy only about 10% would be feasible for a nephron-sparing surgery. These surgeries carry a risk of leaving behind nephrogenic rest in addition to other procedure related complications. Hence, partial nephrectomy is recommended for patients with synchronous or metachronous bilateral tumors, tumors in solitary kidneys and children with risk of multiple neoplasms such as in BWS.

Chemotherapy

The current first-line drugs for WT are vincristine, dactinomycin and doxorubicin, used according to the stage. The second-line drugs for nonresponsive, relapse disease are ifosfamide, etoposide, carboplatin and cyclophosphamide. The chronology for deliverance of chemotherapy and the drug combination and duration differs among the cooperative groups, which however, has been refined over successive trials to optimize survival rates while minimizing acute and long-term toxicities. Noteworthy is despite these differences the survival results among all group is similar (**Tables 7 to 9**). The SIOP and UKCCSG group has favored the use of preoperative chemotherapy in attempt to down stage the tumor, whereas the NWTSG advocates upfront nephrectomy without preoperative therapy in order to precisely identify the tumor stage.

The NWTSG and SIOP approaches to WT treatment each have distinct advantages and disadvantages. The former approach allows an accurate assessment of histologic diagnosis and
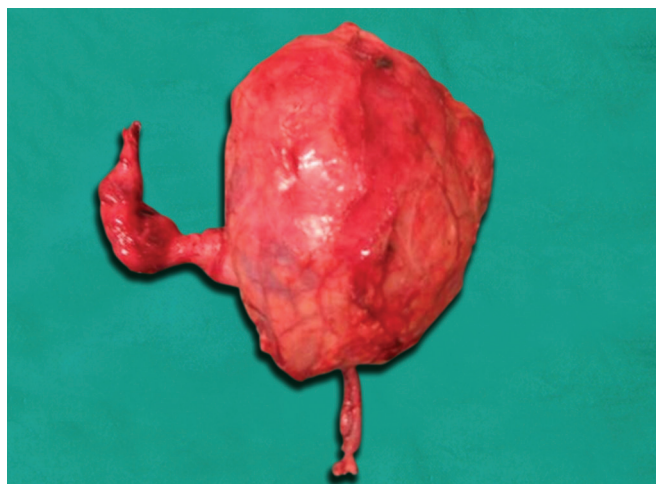
Figure 4 Nephrectomy specimen with tumor thrombus removed en-bloc

Table 7 National Wilms tumor studies-5 (NWTS-5) outcomes for favorable histology Wilms tumor

Stage	4-year EFS (%)	4-year OS (%)
I	92.4	98.3
II	81.4	97.6
III	88.7	94.8
IV	74.6	86.3

Abbreviations: EFS, event-free survival; OS, overall survival.

Table 8 National Wilms tumor studies-5 (NWTS-5) outcomes for unfavorable histology Wilms tumor

Stage	4-year EFS (%)	4-year OS (%)
I	69.5	82.6
II	82.6	81.2
III	64.7	66.7
IV	33.3	33.3

Abbreviations: EFS, event-free survival; OS, overall survival.

Table 9 International Society of Pediatric Oncology (SIOP) 93-01 outcomes for low and intermediate risk Wilms tumor

Stage	5-year EFS (%)	5-year OS (%)
I	88.3	97
II	91	96
III	84	91
IV	76.8	86.7

Abbreviations: EFS, event-free survival; OS, overall survival.

tumor extent and also enables the collection of untreated tumor for biology studies and provides an unadulterated view of the tumor's molecular biology. The SIOP approach also leads to a low incidence of perioperative tumor rupture (7%) and histologic response to chemotherapy can be assessed postoperatively which provide valuable prognostic information. However, in the SIOP studies, neoadjuvant chemotherapy was commenced without histologic proof, resulting in chemotherapy being given for non-WT or nonmalignant lesion.

Radiotherapy

As a result of the NWTSG and SIOP studies the role of radiotherapy has been customized though not eliminated. Radiation was an important treatment modality in preoperative and adjuvant settings in the earlier studies. With subsequent refinement in therapy with an aim in maximizing cure and reducing morbidity, there are now precise indications for adjuvant radiotherapy. The current standard dose for flank/abdominal irradiation is 10·8 Gy in six fractions and 12 Gy in eight fractions for pulmonary metastases.

Management of Lung Metastases

The SIOP group advocates omission of radiotherapy for patients whose lung metastases disappear completely after 6 weeks of prenephrectomy chemotherapy with vincristine, dactinomycin, and doxorubicin. If the metastases persist, metastatectomy is performed if feasible otherwise the chemotherapy is changed to alternating etoposide/carboplatin and ifosfamide/doxorubicin. Radiotherapy is offered only if there is residual disease after 9 weeks of therapy or with high risk histology of the primary tumor. With this strategy, the 5-year event free survival (EFS) and overall survival

(OS) was 73% and 82% respectively and pulmonary radiotherapy was only given to 14% of patients. The SIOP 2001 study investigated the treatment of CT only pulmonary nodules with chemotherapy stratified for localized or for metastatic disease. There was no significant difference in outcome between the two treatment methods. However, the outcomes of CT only pulmonary nodules were significantly inferior to true unilateral localized disease and not significantly different from those with true metastatic disease signifying a complex implication on therapy for CT only pulmonary nodules.

The NWTSG continues to administer whole lung irradiation in patients with pulmonary metastases detected on chest radiographs. For CT only pulmonary nodules the NWTS analysis revealed better EFS and not OS with addition of doxorubicin and no benefit of pulmonary radiation.

Customized Approach for Therapy

There is an incessant dilemma regarding the choice between up-front nephrectomy and preoperative chemotherapy. The evidence available through the randomized study from the cooperative groups provides the opportunity to have a customized approach according to the available resources. A simple way is to preselect patients for either SIOP or the NWTS approach based on clinical and imaging findings. Tumors that are potentially operable without difficulty can be identified by documenting small tumors (< 1,000 cc) with completely intrarenal/intracapsular location, absence of thrombus or if present, not beyond the renal vein, absence of lymphadenopathy, metastases and a normal contralateral kidney. Such patients may be subjected to up-front surgery. Locally advanced disease with perinephric spread, extensive adenopathy, and silent peritoneal deposits can be offered preoperative chemotherapy which offsets lack of surgical expertise and makes treatment of WT more widely applicable (**Fig. 2**). In these patients, an image guided biopsy can also be performed to confirm the diagnosis of WT. The postoperative treatment should be based on the stage and histology as per the policies of the respective group.

PROGNOSTIC FACTORS

The important prognostic determinants which impact on treatment selection and oncological outcome are given below:

Tumor Stage

Tumor stage is the original prognostic factor for WT. The difference between SIOP and NWTS is that the staging is performed after upfront nephrectomy in the latter and after preoperative chemotherapy in the former. The distinct advantage of preoperative chemotherapy is the downstaging of local stage, with only 40% being stage II or III, compared to 58% in the NWTS-5 study.

Histology

Tumor histology is the most powerful prognostic factor for WT. The NWTSG categorize anaplasia, present in 5–10%, as UH. Augmentation of therapy has resulted in improved outcomes; however, it remains inferior to the outcomes of FH WT. The SIOP group in addition to anaplasia have identified residual blastemal histologic type, present in 10%, associated with adverse outcomes and have augmented treatment with subsequent good results in the latest SIOP 2001 study.

Loss of Heterozygosity at Chromosome 1p and 16q

Loss of heterozygosity (LOH) at chromosome 1p and 16q was prospectively analyzed by NWTS-5. Tumor-specific LOH for both

chromosomes was found in approximately 5% of patients with FH WT and was associated with increased risk of relapse and death. Therapy was augmented in recent Children's Oncology Group (COG) studies for patients with LOH 1p and 16q, the results of which are pending.

Age and Tumor Weight

The NWTS-5 has identified a very low risk WT, which can be treated with surgery alone. It includes children with Stage I-FH WT younger than 24 months and whose nephrectomy specimen weighed less than 550 g. Relapses in these patients could be successfully salvaged with chemotherapy without affecting the OS.

Response to Preoperative Chemotherapy

Response to preoperative chemotherapy identifies the favorable low-risk group with good prognosis and the unfavorable blastemal histologic type with poor prognosis.

Completeness of Lung Nodule Response

Clearance of pulmonary metastasis after chemotherapy with or without metastatectomy, results in significantly better outcome than those who do not achieve clearance.

Tumor Volume

Tumor volume after preoperative therapy showed a significantly better outcome for smaller tumors compared to larger tumors as a result of which patients with tumors greater than 500 mL after preoperative chemotherapy were categorized to high risk and intensification of therapy in Germany.

Long-term Sequel

With long-term follow-up data being available in a large number of survivors of WT, the long-term sequel of treatment are becoming better defined. Renal failure after surgical management of unilateral WT is rare (< 1% at 20 years). However, syndromic patients (5–90%) and patients with bilateral disease (14%) are at risk of ends stage renal disease. Cardiac problems secondary to anthracycline administration compounded by whole-lung radiotherapy as well as pulmonary complications secondary to whole lung radiotherapy are real concerns and need to be addressed. Gonadal dysfunction secondary to chemo and/or radiotherapy may occur. Children treated for WT are also at an increased risk of second malignancy, especially if they have also received radiotherapy in addition to chemotherapy.

BILATERAL WILMS TUMOR

Synchronous bilateral WT account for 6% of all WT and pose a special challenge (**Fig. 2**). The goal of therapy for patients with bilateral disease, beyond cure of the tumor, is to spare renal parenchyma to avoid significant renal insufficiency. The treatment of children with bilateral WT must be individualized. Biopsy for confirmation of diagnosis or to detect anaplasia is unnecessary since it is unusual to have a non-WT in bilateral disease and difficult to identify anaplasia. Following 6 weeks of chemotherapy, the patient should be reassessed. If serial imaging studies show no further reduction in tumor, a nephron-sparing surgery should be performed if negative margins can be obtained; otherwise, biopsy should be performed to confirm viable tumor. Nephrectomy is performed when salvage is not possible.

Metachronous tumors in the contralateral kidney account for 2% of WT, with children younger than 12 months with perilobar nephrogenic rests at a higher risk. The contralateral tumors need to be treated independently as the tumors in the first kidney. Although

patients with metachronous tumors have a worse survival than those with synchronous tumors (5- and 10-year OS of 49.1% and 47.2%); in the former group, those developing after 18 months of initial diagnosis fare better than those developing earlier (10-year OS 55.2% vs. 39.6%). Renal transplantation for children with WT is usually delayed until 1–2 years after completion of treatment for the tumor.

RECURRENT WILMS TUMOR

The most frequent site of relapse is the lungs, followed by the tumor bed. Other intra-abdominal sites, brain and bone are less frequent. A combination of local and distant metastases is also noted. The SIOP group had a relapse rate of 12% and the NWTS group had a relapse rate of 15% in patients with favorable-histology WT. Based on the initial treatment received, which in turn is largely dictated by tumor stage and histology, patients with relapsed WT can be assigned to standard, high and very high-risk group (**Table 10**). The standard risk group is generally salvageable. The NWTS-5 stratum B protocol (surgical resection, radiation therapy, and alternating courses of vincristine/doxorubicin/cyclophosphamide and etoposide/cyclophosphamide), used for the standard risk group had a 4-year EFS and OS rate of 71.1% and 81.8%, respectively. However, high and very-high-risk relapse groups present two areas of specific clinical need. The NWTS-5 stratum C protocol (surgical resection, radiation therapy, and alternating courses of cyclophosphamide/etoposide and carboplatin/etoposide), reported a 4-year EFS and OS of only 42.3% and 48%, respectively, suggesting the need for novel agents for the treatment of relapsed WT. The use of high-dose therapy with stem cell rescue appears attractive however; given that most relapsed WT patients already have some degree of renal compromise and will be receiving nephrotoxic drugs at relapse, there is an important clinical question about whether high dose chemotherapy requiring autologous stem-cell rescue is able to increase overall survival. Pooled analyses of published data of high-dose chemotherapy and stem cell rescue have identified major differences as to relative merits within the three risk groups. Amongst those of Risk I there was a suggestion of a detrimental effect of high-dose chemotherapy in terms of EFS, a marginal but potentially worthwhile advantage for those of Risk II and a considerable advantage for Risk III.

Table 10 Risk categories for relapsed Wilms tumor (WT)

Standard risk: Based on initial treatment received	*V/VA:* No RT
High risk: Based on initial treatment received	V/VA with RT VAD with or without RT Substitution with ifosfamide or cyclophosphamide
Very high risk: Based on stage and histology, initial treatment received or prior relapse	Stage IV disease with unfavorable histology Received at least 4 chemotherapy agents Further relapse or progression after first relapse

Abbreviations: V, vincristine; A, actinomycin-D; D, doxorubicin.

IN A NUTSHELL

1. Wilms tumor accounts for 6% of all pediatric malignancies. It affects predominantly children less than 5 years of age.
2. A judicious decision for biopsy at presentation should be taken considering operability and general condition of the patient.
3. The histologic grade and stage of the tumor are the most important determinants of treatment and outcome in Wilms tumor.
4. Prevention of tumor spillage and lymph node sampling are extremely important in accurate staging and therefore appropriate treatment.
5. There are two major staging systems used, a forthright, surgery-based system developed by the NWTSG; and a delayed surgery-based system developed by SIOP.
6. The chronology for deliverance of chemotherapy and the drug combination and duration also differs among the cooperative groups which has been refined over successive trials to optimize survival rates while minimizing acute and long-term toxicities.
7. Despite the different treatment approaches, the survival results of NWTSG and SIOP are similar.
8. The most frequent site of relapse is the lungs and based on the initial treatment received the relapses can be assigned to standard, high and very high-risk group.

MORE ON THIS TOPIC

Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms' tumor: Results from the fifth National Wilms' Tumor Study. J Clin Oncol. 2006;24:2352-8.

Graf N, van Tinteren H, Bergeron C, et al. Characteristics and outcome of stage II and III non-anaplastic Wilms' tumour treated according to the SIOP trial and study 93-01. Eur J Cancer. 2012;48:3240-8.

Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2005;23:7312-21.

Grundy PE, Green DM, Dirks AC, et al. Clinical significance of pulmonary nodules detected by CT and not CXR in patients treated for favorable histology Wilms tumor on National Wilms Tumor Studies-4 and 5: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012;59:631-5.

Kalapurakal JA, Dome JS, Perlman EJ, et al. Management of Wilms' tumor: current practice and future goals. Lancet Oncol. 2004;5:37-46.

Malogolowkin M, Cotton CA, Green DM, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer. 2008;50:236-41.

Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist. 2005;10:815-26.

Shamberger RC, Anderson JR, Breslow NE, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. Ann Surg. 2010;251:555-8.

Smets AM, van Tinterin H, Bergeron C, et al. The contribution of chest CT-scan at diagnosis in children with unilateral Wilms tumour. Results of the SIOP 2001 study. Eur J Cancer. 2012;48:1060-5.

Verschuur A, van Tinteren H, Graf N, et al. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol. 2012;30:3533-9.

Chapter 45.10
Brain Tumors

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Central nervous system (CNS) tumors account for nearly 20% of all neoplasms in children under-15 years of age. They are the second most common form of pediatric cancer, exceeded only by leukemias. Brain tumors remain the leading cause of cancer deaths in pediatric oncology patients. They differ from adult tumors in some important respects (**Table 1**).

EPIDEMIOLOGY

The overall incidence of CNS tumors is 3–5 new cases per 100,000 (Children < 15 years) per year, which is constant throughout the world. Children under-5 years of age have the greatest incidence of brain tumors with primary CNS tumors being the most common in the first decade of life. 25% of all pediatric brain tumors present before the age of 5, and 75% before 10 years of age.

There is limited data from India describing their epidemiology. In a recent large multi-institutional study from India, the most common primary pediatric brain tumors were astrocytic tumors (34.7%), followed by medulloblastoma and supratentorial primitive neuroectodermal tumors (PNETs, 22.4%), craniopharyngiomas (10.2%) and ependymal tumors (9.8%). The most common astrocytic tumor was pilocytic astrocytoma. Except for a slightly higher frequency of craniopharyngiomas, the histological profile of pediatric brain tumors in India was similar to that reported globally. The drawback to interpreting this study information is that it is not a population-based data and the information is collated from neuropathology reports thus excluding CNS tumors diagnosed on the basis of radiology only (**Fig. 1**).

ETIOLOGY

The etiology of pediatric brain tumors remains largely unknown. They can be broadly classified as those associated with certain genetic conditions (**Table 2**), which accounts to 5% and even fewer to those predisposed from environmental factors (**Table 3**). For most patients, no predisposing factors are as yet apparent.

Table 1 Salient features of pediatric central nervous system tumors

• Primary brain and spine tumors outnumber metastatic brain tumors in children
• A greater proportion of pediatric tumors are:
– Infratentorial in location except in infancy
– Low grade gliomas (hemispheric high grade gliomas are rare in children)
– Besides gliomas, other major tumor types including the primitive embryonal neoplasms are also common. Medulloblastoma is the most common malignant brain tumor in children
• Gross total or near total excision has clearly been shown in many tumor types to improve prognosis
• Pediatric brain tumors (especially embryonal tumors) are more responsive to chemotherapy than adult tumors
• Radiotherapy is cautiously used in children in view of significant late effects of therapy
• On the whole, the long-term prognosis is better in children than adults

CLASSIFICATION

Pediatric brain tumors can be categorized as summarized in **Table 4**. The World Health Organization (WHO) classification is the most widely accepted classification and uses histological type and grading as a basis for classification of CNS tumors (**Tables 5 and 6**). The brain is composed of two main cell types namely the neurons and the glial cells. Both arise in early development from primitive neural ectoderm. The majority of primary brain tumors arise from glial cells and are broadly termed *gliomas*. Gliomas can be further divided as by glial subtypes: astrocytes (astrocytoma), oligodendrocytes (oligodendroglioma), ependymal cells (ependymoma), and microglia. Blastomas are malignant tumors whose cells have undeveloped or embryonic characteristics. Although the WHO classification is applicable to pediatrics, tumors showing mixed lineage of neuronal and glial elements are difficult to categorize. Additionally the classification does not separate tumor types on the basis of tumor location (supratentorial versus infratentorial) which has significant implications on clinical presentation and management.
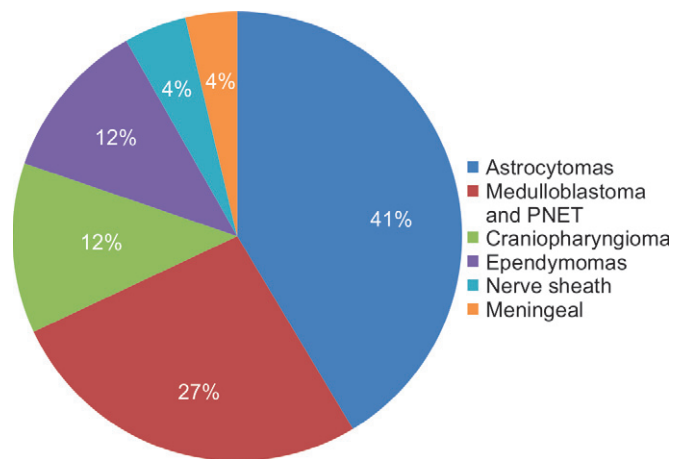
Figure 1 Incidence of pediatric brain tumors in India
Source: Jain A, Sharma MC, Suri V, et al. Spectrum of pediatric brain tumors in India. Neurol India. 2011;59:208-11.

Table 2 Hereditary associations of pediatric brain tumors

Hereditary disorder	Associated brain tumor
Neurofibromatosis type I	• Visual pathway gliomas • Low grade astrocytomas involving diencephalon, cerebral hemispheres and posterior fossa
Neurofibromatosis type II	• Schwannomas • Gliomas • Ependymomas especially spinal ependymomas
Tuberous sclerosis	• Subependymal giant cell astrocystomas
Li-Fraumeni syndrome	• Gliomas both high grade and low grade • Medulloblastomas • Supratentorial primitive neuroectodermal tumors • Choroid plexus tumors
Gorlins syndrome (Nevoid basal cell carcinoma)	• Medulloblastomas
Turcots syndrome	• Gliomas • Medulloblastomas

Table 3 Environmental etiological factors associated with pediatric brain tumors

Etiological factor	Associated risk of brain tumor
Ionizing radiation including cranial irradiation	• High dose radiation exposure is the most established environmental risk for pediatric brain tumors namely high grade astrocytomas and meningiomas • Children who have cranial irradiation for acute lymphoblastic leukemia (ALL) have a seven-fold increased risk of developing any type of second cancer, and a twenty-two fold increase in CNS neoplasms
Tobacco	• Preconceptional paternal smoking may be linked to development of pediatric brain tumors • Cancer in the offspring of male smokers may be due to DNA damage or DNA-adduct formation in the sperm
Low frequency electromagnetic field	• Initial studies suggested an increased association but other studies have not confirmed it
Infectious agents	• No consistent correlation between an infection and pediatric brain tumors • Maternal exposure to polyomaviruses like Simian virus 40, JC virus and also herpes virus may be an inciting event in the development of pediatric brain tumors
N-nitroso compounds	• Maternal ingestion of N-nitroso compounds or their precursors may increase risk of pediatric brain tumors • This includes nitrite-cured and smoked meat, fish, cheese, and beer • The nitrosation process can be inhibited by vitamins C and E
Maternal medications	• Methoxyflurane, an inhalational anesthetic has been associated with brain neoplasms
Immunosuppression	• Acquired immunodeficiency like in post-transplant recipients, HIV carriers and also primary disorders like ataxia telangiectasia and Wiskott-Aldrich syndrome have been associated with CNS lymphomas • Epstein-Barr virus may have a facilitating role in this situation
Vitamins	• Maternal ingestion of folate, vitamin C, and vitamin E are all associated with a decreased risk of pediatric brain tumor • Folate plays a protective role from development of neural tube defect • A common mechanism for the development of neural tube defects and PNETs has been suggested, suggesting that folate may also play a role preventing the latter

Abbreviations: PNET, primitive neuroectodermal tumor; CNS, central nervous system; HIV, human immunodeficiency virus; DNA, deoxyribonucleic acid.

Table 4 General classification of brain tumors

Tumor pathology	Location	Origin
• Grade (high grade or low grade) • Histological classification (World Health Organization [WHO]) • Benign or malignant	• Supratentorial versus infratentorial • Intra-axial versus extra-axial	• Primary • Secondary

Roughly 60% of all childhood brain tumors are infratentorial and arise in the posterior fossa. The most common of these are medulloblastoma, low-grade astrocytomas of the cerebellum, ependymomas and brainstem tumors. Supratentorial tumors include hemispheric astrocytomas, ependymomas, craniopharyngiomas, germ cell tumors, supratentorial PNET, etc. Tumors can also be categorized in relation to the leptomeninges as intra-axial (tumors arising inside the pia-arachnoid) and extra-axial (tumors arising outside the pia-arachnoid). Pediatric brain tumors can also be categorized on the basis of site of origin of the space occupying lesion. Unlike adults where majority of brain tumors are secondary metastasis, in the pediatric age group primary CNS tumors predominate.

MOLECULAR GENETICS OF BRAIN TUMORS

With recent advances in understanding the molecular biology of pediatric brain tumors and with advent of high throughput genetic screening, the risk stratification has undergone major changes. This has had a profound impact on the diagnosis, treatment and prognosis of childhood brain tumors and has led to the advent of targeted therapies in pediatric brain tumors especially medulloblastoma (**Table 7**).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In pediatric population, early diagnosis requires a high level of clinical suspicion and acumen.

The clinical presentation is dependent not only on the location of the tumor but also on the age of the patient and the rapidity and pattern of growth of the tumor. Symptoms and signs of brain tumors can result from raised intracranial pressure and/or from focal effects of the tumor on neighboring neural structures (**Table 8**).

Differential Diagnosis

The differential diagnosis of brain tumors includes other intra-cranial mass lesions, hydrocephalus, intracranial hemorrhages and infections. Pseudotumor cerebri, lead encephalopathy and other myriad causes of brain edema should be excluded.

Neuroradiology

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has revolutionized the approach to a child with suspected intracranial tumors. The MRI is superior to computerized tomography (CT) scans due to its unique multiplanar capabilities, which offer detailed anatomical information with superior resolution and sensitivity. It is also superior for its posterior fossa localizations, because it is free from bony artifacts. MRIs are useful for making a preoperative diagnosis and for planning the treatment which could include image guided therapies like surgery, chemotherapy and radiotherapy. It also is useful for prognostication and disease progression and also for early diagnosis of other effects like leukoencephalopathy, secondary tumor development, ischemic and hemorrhagic complications, postradiation necrosis along with mineralization. Thus, MRI preferably with fluid attenuation inversion recovery (FLAIR) sequence is now an essential tool for assessment of pediatric brain tumors. The other specialized MRI applications include:
- *MRI with gadolinium contrast:* To evaluate the degree of enhancement, intratumor architecture and dissemination.
- *Magnetic resonance venography and magnetic resonance angiography:* To depict the extent of vascular involvement.
- *Magnetic resonance perfusion imaging:* To study the cerebral perfusion dynamics.

Table 5 World Health Organization (WHO) histological classification of tumors of central nervous system

Neuroepithelial tissue tumors	Astrocytic tumors	• Astrocytoma (Grades 1 and 2) • Anaplastic astrocytoma • Pilocytic astrocytoma • Pleomorphic xanthoastrocytoma • Pilomyxoid astrocytoma • Subependymal giant cell astrocytomas • Glioblastoma multiforme
	Oligodendroglial tumors	• Oligodendroglioma • Anaplastic oligodendroglioma
	Ependymal tumors	• Ependymoma (Grade II) • Anaplastic ependymoma (Grade III) • Myxopapillary ependymoma
	Choroid plexus tumors	• Choroid plexus papilloma • Choroid plexus carcinoma
	Neuronal and mixed neuronal glial tumors	• Gangliocytoma • Ganglioma • Desmoplastic infantile neuroepithelioma • Dysembryoplastic neuroepithelial tumor (DNET)
Embryonal tumors	Primary neuroectodermal tumors (PNETs)	• Medulloblastoma • CNS neuroblastoma • Ependymoblastoma • Supratentorial PNET medulloepithelioma
	Other embryonal cell tumors	• Pineoblastoma • Atypical teratoid rhabdoid tumors
Germ cell tumors	• Germinoma • Embryonal carcinoma • Endodermal sinus tumor • Choriocarcinoma • Teratoma • Mixed germ cell tumors	
Sellar region	• Craniopharyngiomas • Pituitary adenoma • Pituitary carcinoma	
Metastatic tumors	• Leukemia • Lymphoma • Histiocytosis • Neuroblastoma • Sarcomas • Rhabdoid tumors	

Table 6 World Health Organization (WHO) grading of tumors

Grade I: Low proliferative potential and possibility of cure with surgical resection alone
Grade II: More infiltrative and have a likelihood of recurrence and potential to progress
Grade III: Histological evidence of malignancy and less likely to be cured by surgery alone
Grade IV: Most cytologically malignant and mitotically active tumors

- *Functional MRI (fMRI)*: Blood oxygenation dependent technique (BOLD) is used which is dependent on the state of oxygenation of hemoglobin during brain activity. It helps identify eloquent regions of the brain when a surgery is planned.

- *Magnetic source imaging (MSI)*: It correlates anatomic data from a conventional MRI along with electrophysiological data from a magnetoencephalography and helps in guiding the surgical approach to tumors.
- *Diffusion imaging (DI):* It can reflect cellular density and microarchitecture with the apparent diffusion coefficient (ADC) inversely correlating with the grade of tumor and cellular proliferation.
- *Diffusion tensor imaging (DTI)*: It provides a visualization of the fiber tract direction which aids in presurgical planning and in assessing treatment induced white matter changes.
- *Magnetic resonance spectroscopy (MRS)*: It provides metabolic information and monitoring of four important brain metabolites namely N-acetyl-aspartate (NAA, marker of neuronal and axonal integrity), choline (cell membrane marker), creatine and phosphocreatine (energy metabolites)

Table 7 Molecular biology/genetics of pediatric brain tumors

Medulloblastomas and supratentorial PNETs	Astrocytomas	Others
• Isochromosome 17q often in combination with loss of 17p seen in 50% of medulloblastomas • Increased expression of *ErbB2* and *MYCC* oncogene • Mutation in Sonic Hedgehog (SHh) pathway in 25% of sporadically occurring medulloblastomas • Notch pathway target gene *Hes1* is seen in 15% of medulloblastomas • Somatic mutations of PATCHED (*PTCH* gene) is seen in Gorlins syndrome *Favorable outcome* • High expression of neurotrophin-3 receptor, TRKC is an independent predictor of favorable outcome in medulloblastomas • Immunoreactivity for beta-catenin, a marker of Wnt pathway activation	• *BRAF* oncogene—activating mutation is seen in pilocytic astrocytomas of the cerebellum and optic pathway • High TP53 expression in malignant gliomas has a poor outcome • Activated PDGF receptors and PTEN deficiency are associated with increasing malignant histology and decreased survival	• *hSNF5/INI1* gene mutations in association with atypical teratoid rhabdoid tumors • Chromosome 17p deletions have been found in 50–80% ependymomas

Abbreviation: PENT, primary neuroectodermal tumors.

and lactate (byproduct of cerebral metabolism). The NAA concentration within the tumor is decreased compared to normal brain tissue while choline concentration is increased in tumors, demyelination and inflammation. MRS thus helps to identify and differentiate tumor types, guide stereotactic biopsies and distinguish active tumor from scars or radiation necrosis.

Molecular Imaging
Molecular imaging like the single photon emission computerized tomography (SPECT) and positron emission tomography (PET) assess the metabolic activity in brain tumors. PET with radiotracers like fluorodeoxyglucose (FDG) is used for evaluation of regional cerebral glucose metabolism. Whole body PET is also useful for picking up the primary tumor site that may have led to metastatic lesions in the brain.

Computerized Tomography
It is useful in assessing acute neurological presentations, hemorrhage and intracranial calcifications.

Ultrasound
In infants, before the fontanel is fused, ultrasound scanning can be used to rule out intracranial masses, however, it is inadequate for posterior fossa lesions.

Neurophysiology
The electroencephalogram (EEG) is requested if the patient has seizures and altered sensorium. Evoked potentials both auditory and visual may be ordered when pressure on the auditory and visual pathway is expected. A visual evoked potential (VEP) is commonly needed in a patient with visual loss secondary to a chiasmatic lesion or hydrocephalus, while auditory evoked potentials are needed in suspected cerebellopontine angle tumors.

MANAGEMENT PRINCIPLES

Surgery
Surgery, where feasible is generally the primary treatment for the majority of childhood CNS tumors. The gross total resection is an important factor in determining outcome and is associated with a better survival rate especially in children less than 5 years of age. In situations where complete resection is not possible, partial resection is useful to debulk the tumor, thus, allowing the remaining tumor to be treated with other forms of adjuvant therapy. For some tumor types like low-grade gliomas, surgery may be curative and obviate the need for alternate therapies.

Corticosteroid therapy may be necessary preoperatively in some patients with large tumors to reduce associated cerebral edema. After removal of the tumor and the placement of a temporary drain, about 30% of patients may not re-establish the normal cerebrospinal fluid (CSF) pathways and will need a permanent internal (VP) shunt because of permanent hydrocephalus especially with posterior fossa tumors. Shunting should not be routine and seeding of metastasis and postsurgical infection are two complications best avoided. Modern techniques have reduced significant operative morbidity to below 5%. Surgery in the suprasellar region may be associated with visual impairments and also significant disruption of the hypothalamic-pituitary axis. Posterior fossa surgery has its own associated complications which include cerebellar mutism, cranial nerve palsies, pseudobulbar palsy, pseudomeningocele and hydrocephalus.

Radiation Therapy
The aim of the therapy is to achieve selective tumor cell death with as little damage to the surrounding brain. Craniospinal axis radiation therapy (CSA-RT) which involves treatment of the whole brain and spine including the meninges is used for brain tumors like medulloblastoma, embryonal tumors and germ cell tumors, which are prone to leptomeningeal spread. Low grade supratentorial astrocytomas, ependymomas and brainstem gliomas usually do not seed the CSF and thus need just focal radiation to the tumor. However, the major morbidity of craniospinal radiotherapy is from long-term effects on normal brain development and cognition. Hence, this is best avoided in children less than 3 years of age. Focal radiotherapy however can be used even in children as young as 2 years in cases of high-grade malignancies. For low-grade gliomas which are not operable chemotherapy, is the preferred mode of primary treatment in young children and radiotherapy is used as a salvage modality.

With evolving technologies, hyperfractionation, radiosensitization, proton therapy, etc., are currently being studied in pediatric brain tumors to allow maximum benefit with minimal toxicity to normal cells. Conventional radiotherapy can cause various acute and subacute side effects which include headache, nausea, vomiting, worsening of neurological deficits, somnolence, alopecia skin erythema, etc. They also can cause significant late effects following treatment which are discussed subsequently.

Table 8 General overview of central nervous system (CNS) tumor presentation

Raised intracranial pressure Due to • Obstruction of the ventricular system • Mass growing within a fixed cranial volume	*Headache* It is one of the most common pediatric complaints. Headaches which are intense, aggravated by coughing, sneezing, straining, relieved by vomiting, persistent or progressive and which awaken the patient at night are all suggestive of raised intracranial pressure *Vomiting* Usually but not always associated with headaches. Vomiting is projectile, repetitive, and persistent particularly noted in the morning Irritability, lethargy, anorexia, weight gain or weight loss, changes in behavior or school performance *Papilledema* Although a major sign, it is absent in almost half the children with brain tumors especially supratentorial tumors. It should be distinguished from pseudopapilledema, a congenital abnormality of excessive glial proliferation and drusen of the optic nerve head Early signs of papilledema is an increase in the blind spot or loss of color vision. These signs should be sought as most children cannot express visual complaints. Optic atrophy with visual loss are complications of longstanding papilledema **(Fig. 2)** *Cranial nerve abnormalities* Most commonly the 6th cranial nerve is affected. It may be unilateral or bilateral or may fluctuate resulting in diplopia, medial deviation of the affected eye and lateral gaze paresis. Rarely IVth cranial nerve may be involved This can be a "false localizing sign", due to its long course and its proximity to bony structures against which it can get compressed **(Fig. 3)**
Signs of herniation • Downward herniation seen with supratentorial tumors • Upward herniation seen with posterior fossa tumors and tonsillar herniation through foramen of magnum • They are suggestive of acute neurological emergency	3rd cranial nerve palsy produces unilateral pupillary dilatation Paroxysmal stiffness with rigid extension, so called cerebellar fit of Jacksonian can be seen Early tonsillar herniation manifests with head tilt and neck stiffness due to irritation of cervical nerve roots Syndrome of rostrocaudal deterioration results in progressive functional impairment, involving the diencephalon, midbrain, pons and medulla in succession with eventual death
Localizing symptoms and signs due to tumor invasion into normal structures (Most tumors are compressive rather than destructive)	*Optic pathways* • Visual loss *Cerebellum* • Ataxia • Defects in coordination • Nystagmus • Abnormal speech *Brainstem* • Cranial neuropathy • Long tract signs *Supratentorial brain* • Hemiparesis/limb weakness from cerebral cortex involvement • Hemisensory loss • Visual field abnormalities • Cognitive/learning difficulties • Seizures *Deep midline tumors* • Endocrinopathies • Visual acuity and visual field abnormalities • Parinauds syndrome (paralysis of upgaze, loss of pupillary reflex to light, eyelid retraction and nystagmus)
Nonlocalizing symptoms and signs	• Seizures—focal or generalized • General malaise • Changes in behavior • Loss of previously acquired developmental milestones
Early soft symptoms and signs	• Visual inattention • Clumsiness • Decreased energy levels • Mild gait abnormalities like stiffness of gait and decreased arm swing • Pronator drift • Flattening of the nasolabial folds

Figure 2 Papilledema with swelling and hemorrhage of the optic disc on fundoscopy
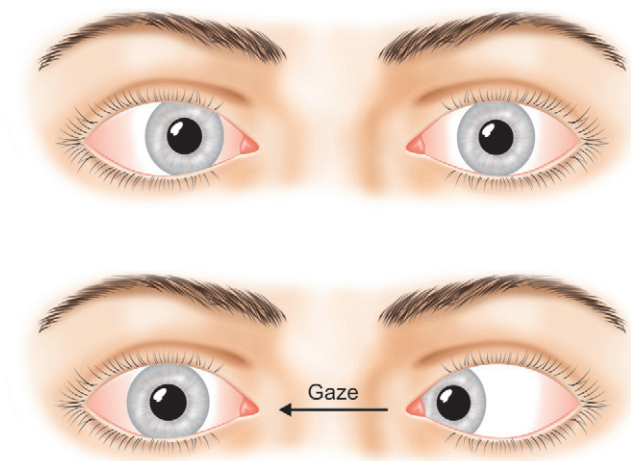
Figure 3 VI left cranial nerve palsy

Chemotherapy

Chemotherapy is an integral component of the multimodality treatment in many pediatric brain tumors. In general, chemotherapy is used for faster growing tumors and in very young children where radiotherapy is generally avoided or delayed to minimize the late effects of therapy. Chemotherapy can be given orally, intravenously, intrathecally or intraventricularly. Some types of brain tumors, such as medulloblastoma, PNET, germ cell tumors respond well to chemotherapy. In children less than 3 years, chemotherapy maybe the only adjuvant treatment used in these tumors and radiation therapy may be avoided during primary treatment to minimize late effects of therapy.

There are various chemotherapy regimens in use and the drugs commonly used to treat pediatric brain tumors include vincristine, cyclophosphamide (or ifosfamide), temozolamide, cisplatin (or carboplatin) etoposide, lomustine and methotrexate. In low-grade gliomas, if residual disease remains after excision then chemotherapy has been used to good effect. The goal of high dose chemotherapy is effectively increasing the delivery of cytotoxic agents to the tumor by overcoming the limited permeability of the blood brain barrier and to overcome drug resistance. The side effects of chemotherapeutic agents are well known and numerous, but are usually short-term. Specific side effects of drugs like hearing loss and nephrotoxicity (associated with cisplatin and carboplatin), neuropathy (vincristine induced) need to be anticipated and detected early.

Newer modalities of therapy such as immunotherapy (administration of cytokines, tumor specific T-cells, cancer vaccines, etc.) and gene therapy are undergoing clinical trials and may be incorporated into frontline treatment regimens in the future.

LATE EFFECTS SEEN IN CHILDHOOD BRAIN TUMOR SURVIVORS

Although with advent of multimodality management significant improvement in survival has been noted in children with brain tumors, it has become obvious over the past 10–20 years that survivors of childhood cancer are at risk for many significant long-term health risks or *late effects* as a result of this treatment. These health risks vary in severity and may have significant impact on the survivor's quality of life. They can be as follows:

Nervous system The treatment of majority of brain tumors includes radiotherapy which is associated with significant late effects. Chemotherapy can enhance this damage. These effects are as follows: developmental delay; decline in intellectual function; psychological problems with depression; behavior disorders; learning problems and school failure; seizures; neuropathies; leukoencephalopathy; vasculitis and moyamoya disease.

Ocular Cataracts, keratoconjunctivitis sicca and visual impairment.

Auditory Hearing impairment usually high frequency hearing loss secondary to chemotherapy (cisplatin, carboplatin). In younger children, hearing loss greatly impacts development with ineffective communication thereby significantly affecting the quality of life. This can be further augmented by the use of cranial radiotherapy due to cochlear damage.

Endocrine Damage to the hypothalamopituitary axis either due to the primary tumor (suprasellar tumors) or a consequence of radiotherapy. This can lead to panhypopituitarism, slowed growth, hypo- or hyperthyroidism, diabetes, early or late puberty, and infertility.

Miscellaneous These include nephrotoxicity (chemotherapy induced glomerular or tubular dysfunction), musculoskeletal deformities (spine secondary to irradiation), reduced bone density and a small risk of second malignancies.

INFRATENTORIAL TUMORS

Medulloblastoma

Medulloblastoma is a primitive neuroectodermal tumor arising in the posterior fossa, and is the most common malignant brain tumor in children (**Figs 4A to F**). These tumors, which arise from the cerebellum (midline more common than hemispherical tumors) are commonly seen in the first decade of life (peak age: 4–6 years, male preponderance). The etiology remains largely unknown with only 1–2% of medulloblastomas associated with tumor syndromes like Gorlins syndrome, Turcots syndrome, etc. The most common oncogenetic factor noted is isochromosome 17q often in combination with loss of chromosome 17p.

Clinical presentation and diagnosis Patients usually present with a short history of symptoms (1–2 months only). The presenting symptoms are generally related to an enlarging primary tumor in the posterior fossa and that of metastatic dissemination in a progressed disease (**Table 9**).

Neuroimaging Medulloblastomas are usually radiographically distinguishable from other posterior fossa tumors on the MRI as the tumor is median, rounded and homogeneous with iso- to
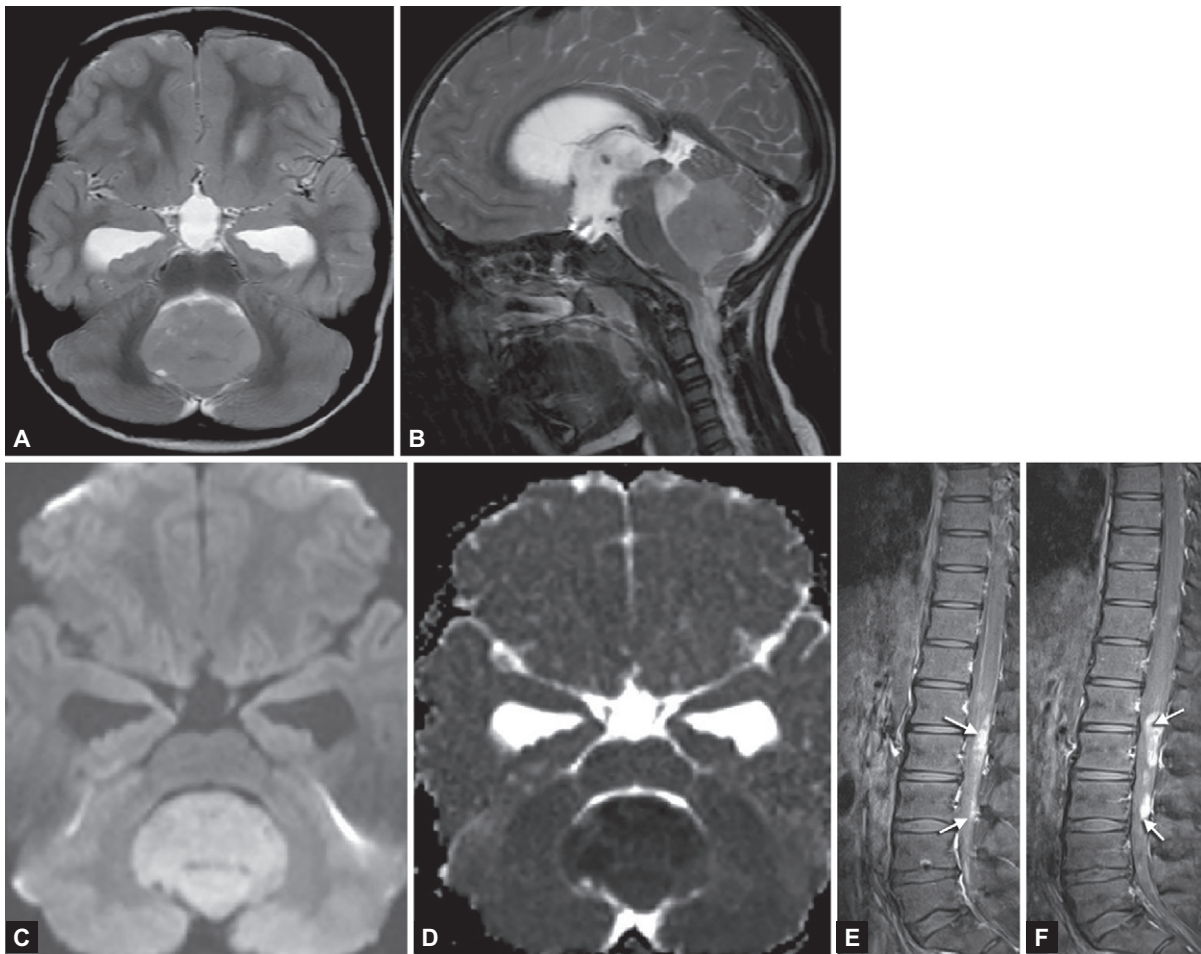
Figures 4A to F Medulloblastoma. (A and B) Axial and sagittal T2-weighted images show a mildly heterogeneous mass in the region of the fourth ventricle. Mass appears isointense to gray matter; (C and D) Axial diffusion weighted images and apparent diffusion coefficient (ADC) maps show decreased diffusion within the same regions of tumor, consistent with high cell density; (E and F) Postcontrast T1-weighted images—sagittal through the spine show nodular enhancement along the surface of the cord, consistent with leptomeningeal dissemination of tumor (arrows)
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

hypointense signal on T1 weighted images and hypointense signal on T2 weighted images. The majority of medulloblastomas are contrast enhanced heterogeneous lesions. It often occupies the fourth ventricle leading to hydrocephalus. Cerebellar hemispheric lesions are less common and usually suggestive of atypical histology (desmoplastic variant).

The multimodality management of medulloblastoma is summarized in **Table 10**.

Prognosis The outlook for children with medulloblastomas has improved in the past few years with a majority of children surviving after treatment. Prognosis depends on various factors such as age (< 3 years portends poor outcome), extent of surgical resection, histologic subtype (classic, large cell or anaplastic, desmoplastic), metastases along craniospinal axis and the molecular subtype (genetics). Surgery with a complete resection, age more than 3 years, nonmetastatic tumor and classic, nodular desmoplastic histologic subtypes are favorable risk factors. Recurrences if any, usually occur during first 2 years post-treatment.

Astrocytomas

Astrocytomas account for nearly 50% of all childhood CNS tumors. They have a peak incidence between 5 years and 6 years and then again at 12–13 years. This is a diverse group of tumors, with several different subgroups and grades. The salient features of this group of tumors are given in **Table 11**.

Cerebellar Astrocytomas

They are the single most common tumor of the posterior fossa. Majority of them are juvenile pilocytic astrocytomas, which classify as low grade astrocytomas. They tend to be well circumscribed and easily amenable to surgical resection. About 80% are cystic tumors with a mural nodule attached to one part of the cyst wall. Solid tumors are less common. Astrocytomas may be rarely diffuse fibrillary subtype in 20% cases and usually seen in the older age group with variable prognosis **(Figs 5A to C)**.

Clinical presentation and diagnosis The clinical features are similar to medulloblastomas but the history is much longer due to the slow growing nature of the tumor. They typically present with hydrocephalus and features of increased intracranial pressure. Parinauds syndrome may be seen with cranial nerve IV palsy, resulting in down and out deviation of the affected eye and often accompanied by a compensatory **head tilt** to the contralateral side. Papilledema is common. School children can present with fatigue, declining academic performance and personality changes.

Table 9 Salient clinical features of medulloblastoma

• Increased intracranial pressure with its classical symptoms. Papilledema is often lacking
• Cerebellar dysfunction which includes truncal ataxia and wide based gait. Nystagmus is conspicuously absent
• Bilateral pyramidal tract signs may be present and wasting is often marked
• Leptomeningeal dissemination can give rise to weakness due to spinal cord or root compression or back pain
• Head tilt and neck stiffness may occur as the result of meningeal irritation due to early cerebellar herniation

Table 10 Multidisciplinary management of medulloblastoma

• Initial surgery—Aim is to:
– Achieve as complete a resection as possible
– Treat the hydrocephalus
Aggressive surgery without any neurodeficit is the ideal first step. The smaller the amount of tumor left behind, more effective are the other modalities
• Radiotherapy following surgery has helped improve survival rates considerably. Neuroaxis radiation (36 Gy for high risk and 23.4 Gy for average risk) with a boost to the tumor bed (18 Gy) is usually undertaken. All children > 3 years undergo this modality of treatment. In children less than 3 years radiotherapy is usually avoided or delayed
• Chemotherapy is generally given after completion of radiotherapy in an adjuvant setting. There are various chemotherapeutic regimens recommended and the drugs commonly used are cyclophosphamide/ ifosfamide, cisplatin/carboplatin, vincristine and lomustine
• Shunting should be considered with caution so as to not provide a bed for metastasis
• Cerebrospinal fluid (CSF) cytology is important to stage medullo-blastoma and usually done after a minimum of 14 days after surgery to avoid false positive results

Neuroimaging They are seen as large mass lesions displacing and compressing the fourth ventricle with associated hydrocephalus. Calcifications are seen in 10–20% of cases. For juvenile pilocytic astrocytomas, T1 weighted images have a low signal intensity and T2-weighted images have a high signal intensity. There is often an enhancing nodule, or enhancing rim of the cystic component of the tumor.

Management and outcome Management is predominantly surgical excision. If an incompletely resected tumor is asymptomatic, the child is generally followed until progression is documented through imaging or neurologic findings as not all incompletely resected tumors progress. Thus, the tumor has an excellent prognosis with 5-year survival rates of greater than 90%. Radiotherapy helps those with incomplete resection and in diffuse astrocytomas. Chemotherapy is usually reserved for younger children in whom radiotherapy can be avoided.

Ependymomas

They constitute 8–10% of intracranial neoplasms in children and arise from the neuroepithelial lining of the ventricles and spinal canal. They are among the most common of the intraventricular tumors along with choroid plexus tumors and colloid cysts. They usually occur in children under-5 years of age. These tumors can occur infratentorial in 60% where they arise in the ependymal lining of the 4th ventricle and obstruct CSF flow. They can extend

Table 11 Classification and salient features of astrocytomas

I. *Low-grade astrocytomas*
• Juvenile pilocytic astrocytomas
– They are WHO grade I tumors and most commonly seen in the posterior fossa and cerebellar in location
– Supratentorial locations can involve the optic pathway, hypothalamic area, thalamus and area around the 3rd ventricle
– Tumors located in the cerebral hemispheres are usually seen in the medial temporal lobes
• Diffuse fibrillary astrocytomas
– It is classified as WHO grade II tumor which is invasive and has a tendency to undergo a malignant change especially in adults
– It is genetically distinct and associated frequently with p53 mutations or occasionally with loss of heterozygosity on chromosome 10p
• Pleomorphic xanthoastrocytoma (PXA)
– It is a form of astrocytoma unique to children and young adults
• Subependymal giant cell astrocytoma
– It presents in early childhood and as early as neonatal period. It has a subependymal origin and occurs along the lining of the lateral ventricles. It is associated with tuberous sclerosis
• Dysembryoplastic neuroepithelial tumor (DNET)
– They are benign tumors and some would argue that these are neuroepithelial tumors rather than gliomas
– On neuroimaging, they are seen as fairly well defined nodules without mass effect or edema
– Majority of patients do well after a surgical resection
The other uncommon low grade astrocytomas include the following:
• Ganglioglioma
• Oligodendroglioma
• Desmoplastic infantile ganglioglioma
II. *High-grade astrocytomas*
They include two main classes of tumors namely
• Anaplastic astrocytomas
• Glioblastoma multiforme
They are rare in children and have a poor prognosis

into the cervical spinal canal and frequently metastasize along the CSF pathways. They can also have a supratentorial location in 30% and spinal in 10% of cases **(Figs 6A to D)**.

Clinical presentation and diagnosis Signs and symptoms of ependymomas are related to the site of origin of the tumor. In general the history is longer than for a rapidly growing tumor like medulloblastoma though distinction is often difficult. Cranial nerve palsies and neck stiffness is more common with ependymomas. Supratentorial ependymomas are generally diagnosed a little earlier than posterior fossa tumors and present with focal cerebral deficit and seizures.

Neuroimaging On imaging a midline mass, often filling the fourth ventricle and associated with hydrocephalus is seen. MRI demonstrates extension of the tumor which appears iso- to hypodense on T1-weighted imaging and hyperdense on T2-weighted imaging. 50% show calcifications. MRI spine to screen for spinal metastasis is a must.
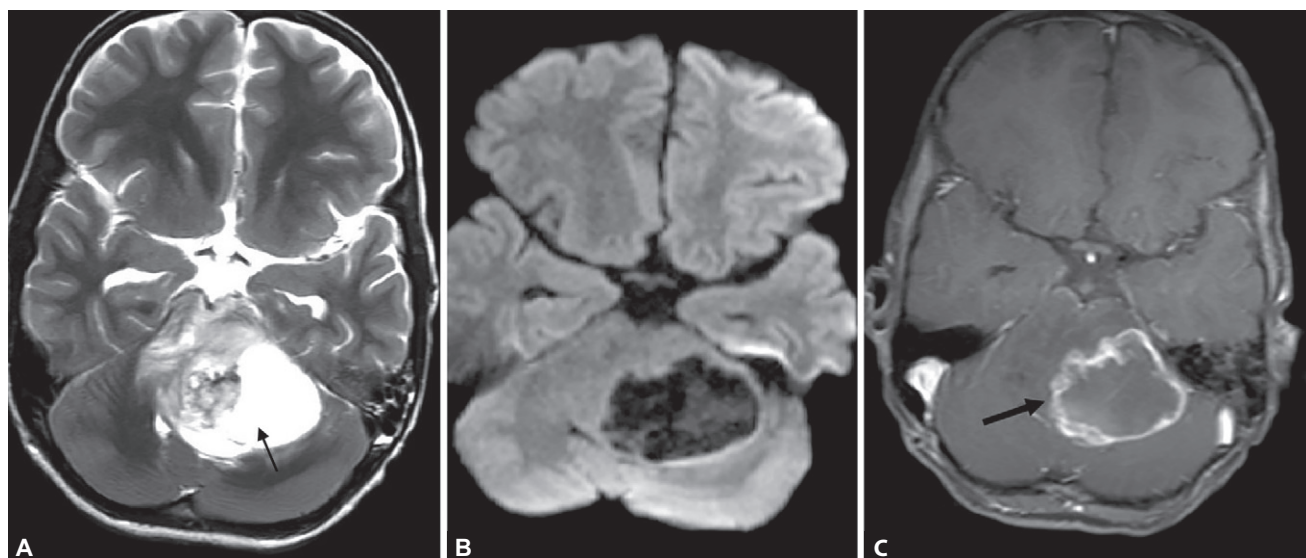
Figures 5A to C Cerebellar astrocytoma. (A) Axial T2-weighted image shows a cystic and solid mass centered in the left cerebellar hemisphere (arrow); (B) Increased diffusion is consistent with the low cellularity of these tumors; (C) Postcontrast axial image showing enhancement of cyst wall (arrow) with minimal enhancement of the solid nodule
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.
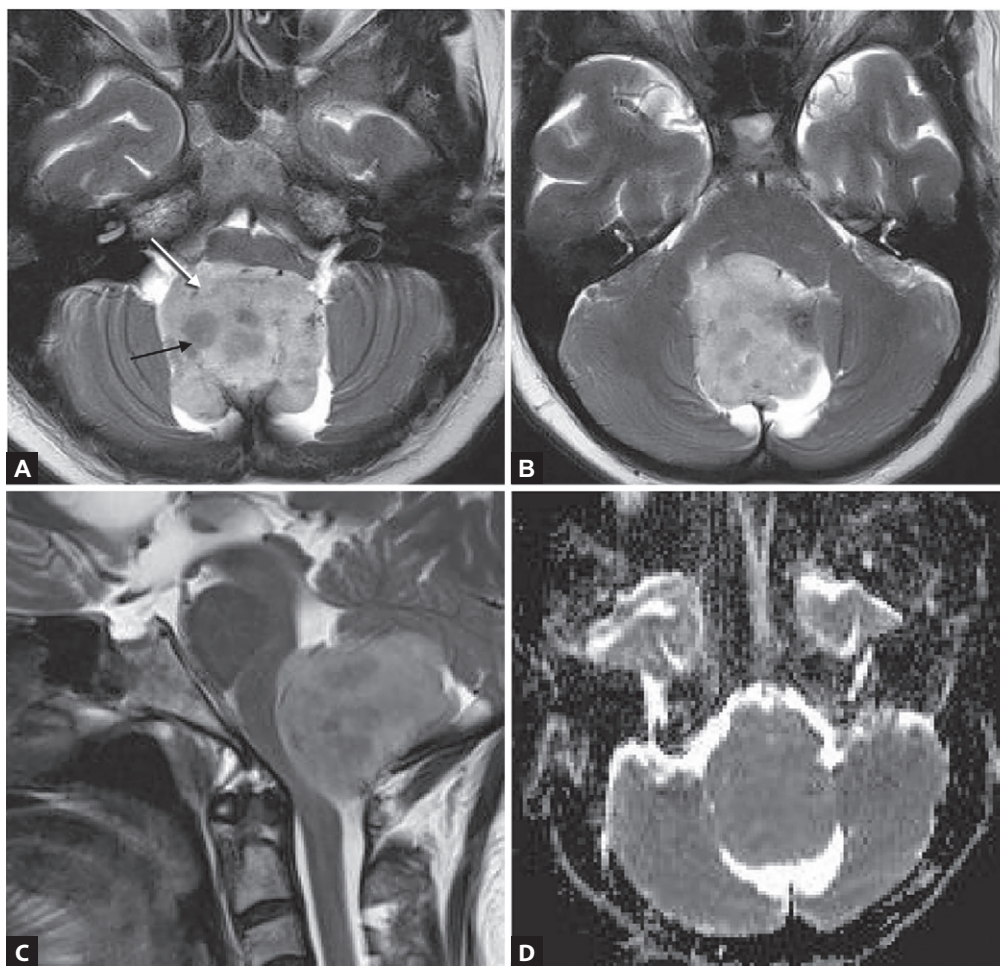
Figures 6A to D Ependymoma. (A To C) T2-weighted axial and sagittal images showing A T2 heterogeneously hyperintense mass (arrows in A) arising from the floor of the fourth ventricle. Hypointense areas seen within the mass indicate intratumoral hemorrhages; (D) The lesion appears isointense on apparent diffusion coefficient (ADC) maps indicating intermediate cellularity of the tumor
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

Management and prognosis Surgery forms an important component of therapy with completely resected tumors having a better prognosis. Many a time, a second look surgery is undertaken in incompletely resected tumors. However, complete macroscopic resection is not always feasible.

Focal radiotherapy to the tumor bed remains the standard postoperative treatment for nondisseminated ependymomas. Craniospinal irradiation is recommended for those with tumor metastasis. Despite several trials, the role of chemotherapy in ependymomas is still undefined. It is presently recommended only for young children (< 3 years) in whom radiotherapy is delayed till they are older.

Brainstem Gliomas

Brainstem gliomas can be diffusely infiltrating tumors or focal tumors **(Table 12)**. Diffuse brainstem gliomas are the leading cause of death in children with CNS neoplasms and survival statistics have remained static over the past 20 years. They are far more common in children and constitute 15–20% of all pediatric brain tumors. The peak incidence is around 6–7 years with a slight male predominance. Diffuse brainstem gliomas (usually pontine in location) are inoperable tumors and are generally treated with radiotherapy. Majority of time, a biopsy is also unwarranted since they have classical features on radiology. Diffuse pontine gliomas have dismal outcomes with survival of less than 10% **(Figs 7A to D)**. The 5-year survival rates vary from 20% to 40% for focal gliomas.

Atypical Teratoid/Rhabdoid Tumors

The tumor is a distinct entity characterized by combination of large rhabdoid cells with a ground glass appearance which express epithelial membrane antigen and vimentin along with occasionally smooth muscle actin, neurofilament protein, glial fibrillary acidic protein and keratin. Germline mutations are seen and if found, siblings should undergo screening for development of kidney or intracranial neoplasms **(Figs 8A to F)**.

Clinical presentation and diagnosis The tumor has an extremely aggressive course with a predilection to the cerebellopontine angle. Multiple cranial palsies can thus be seen.

Neuroimaging The tumor shows on T1-weighted MRI images hyperintense foci within the lesion due to hemorrhage and appear heterogeneous on T2-weighted images. Most of them enhance with contrast agents.

Management and outcome Surgery remains the initial line of treatment with gross total resections associated with a better prognosis. Chemotherapy regimens with early use of local radiotherapy are being considered at various centers. Prognosis in very young children is poor.

SUPRATENTORIAL TUMORS

Supratentorial Primitive Neuroectodermal Tumors

They comprise 2.5–5% of all childhood brain tumors. Most of them arise from the cerebral hemispheres namely the frontal, temporal or parietal lobes, pineal region and rarely from deeper structures like the basal ganglia, diencephalon, etc (**Figs 9A to C**).

Routes of spread They usually spread by local invasion of adjacent tissue although up to 30% may have leptomeningeal spread. Extraneural metastasis is uncommon.

Clinical presentation and diagnosis It is usually abrupt with majority having focal neurologic deficits, including hemiparesis or visual field difficulties. They may present with signs of raised intracranial pressure and other nonlocalizing symptoms like seizures, behavioral alteration and loss of previously acquired milestones.

Neuroimaging The tumor is usually isointense to cortex on FLAIR sequence of MRI and reveals a heterogeneous mass with relatively well defined margins. Enhancement varies from minimum to dense in a heterogeneous or ring like pattern.

Table 12 Comparison of diffuse and focal brainstem tumors

	Diffusely infiltrating	*Focal*
Common site of origin	Pons	Midbrain or medulla
Extent of spread	May spread to medulla or midbrain	Usually circumscribed
Proportion	70–80%	20%
Pathology	Fibrillary astrocytomas Anaplastic astrocytomas Glioblastoma multiforme	Pilocystic astrocytomas Ganglioma
Density (on MRI)	Regions of hypodensity	Lack of hypodensity
Symptoms	• Short duration • Multiple, bilateral cranial nerve deficits (especially VI and VII) • Long tract signs • Ataxia	• Longer duration and depends on tumor location • Palsy of the soft palate • Facial palsy • Pyramidal weakness • Gait ataxia • Dysarthria • Difficulty swallowing
Imaging	Diffuse enlargement of the pons with areas of hypodensity	Pilocytic tumors are better localized and can be exophytic
Management	• Biopsy and partial resection is not warranted because of risk of brain stem damage • Local irradiation to 55–60 Gy is used	• Debulking and resection of cystic component is of value followed by focal radiotherapy
Prognosis	Poor	Variable
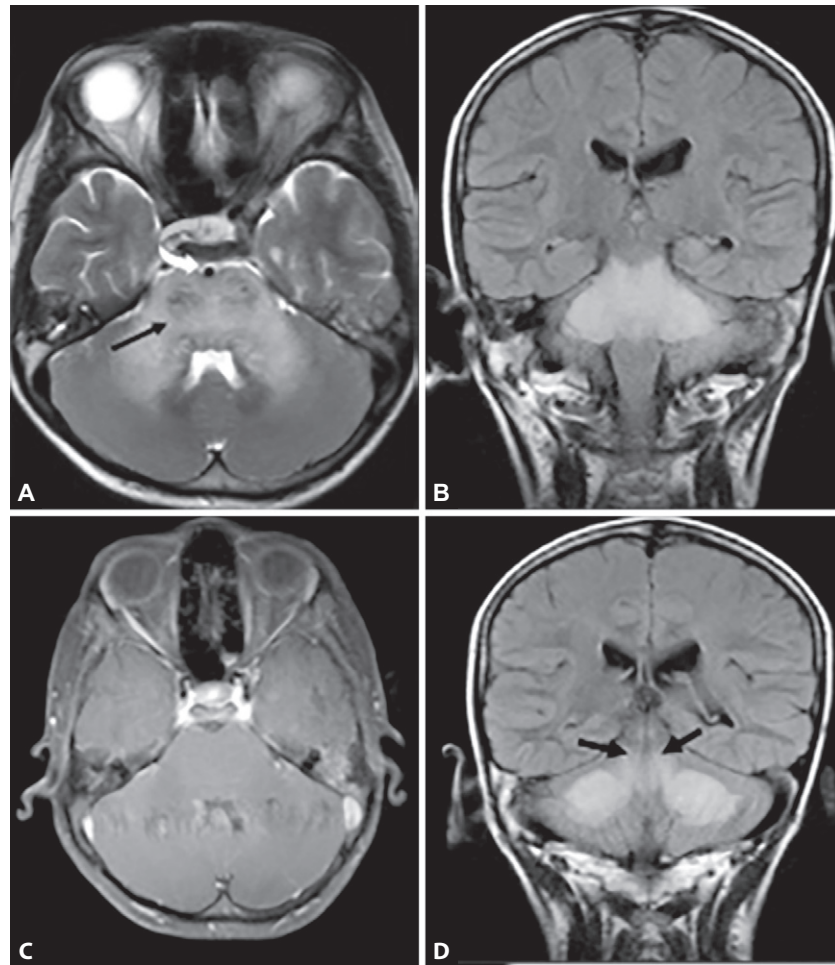
Figures 7A to D Diffuse intrinsic brainstem glioma. (A) Axial T2-weighted image shows an infiltrative, hyperintense mass centered in the pons (arrow) and extending into brachium pontis. Marked expansion of the pons narrows the pontine cistern and engulfs the basilar artery; (B and D) Fast fluid-attenuated inversion recovery (FLAIR) coronal images reveal hyperintense pontine mass involving cerebellar white matter and superior cerebellar peduncles (arrows); (C) Postcontrast T1-weighted axial images show no significant enhancement
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

Management and outcome The initial step in treatment is surgical, followed by radiation and/or chemotherapy depending on the age of the patient. Surgery remains the initial line of treatment with gross total resections associated with a better prognosis. This is followed by radiotherapy and chemotherapy. Treatment approach is along the lines of medulloblastoma. Although histologically they are embryonal tumors like a medulloblastoma, survival outcomes are generally lower.

Optic Pathway-hypothalamic Gliomas
They constitute approximately 5% of all pediatric CNS tumors and are usually juvenile pilocytic astrocytomas. 50% of all gliomas are in association with neurofibromatosis (NF) type I. They can be unilateral or bilateral, involve the chiasma or extend throughout the visual pathway.

Clinical course and diagnosis The signs and symptoms depend on the location and the age of the patient. Anterior lesions, confined to the optic nerve anterior to the chiasm present with mono-ocular visual loss and slowly developing proptosis. Children with posterior lesions present with loss of visual acuity as their presenting complaint. Papilledema and nystagmus suggest a

chiasmatic involvement, whereas blurred discs with visual loss suggest intraorbital lesion. Growth and endocrine involvement may be seen in patients with extensive hypothalamic involvement. The diencephalic syndrome (emesis, failure to thrive, and unusual euphoria) is a classical presentation for infants with hypothalamic gliomas.

Neuroimaging MRIs are useful for assessment of intracranial extension of optic gliomas. The spontaneous density of chiasmatic tumors is close to that of the cerebral tissue, and homogeneous enhancement is seen postcontrast injection.

Management and outcome All patients with clinical suspicion of optic glioma need to undergo an MRI brain and orbit followed by a detailed ophthalmological assessment which includes fundus examination, visual acuity and field of vision along with a VEP. In patients who present with visual loss or in those with progression of visual symptoms and also in patients with a progressive tumor growth or chiasmatic involvement, treatment is indicated. Surgery of optic nerve tumors is rarely undertaken and is usually a globe-sparing procedure done in cases with significant proptosis and vision impairment. Debulking procedures of the optic chiasmatic tumors are also undertaken occasionally especially in cases of large
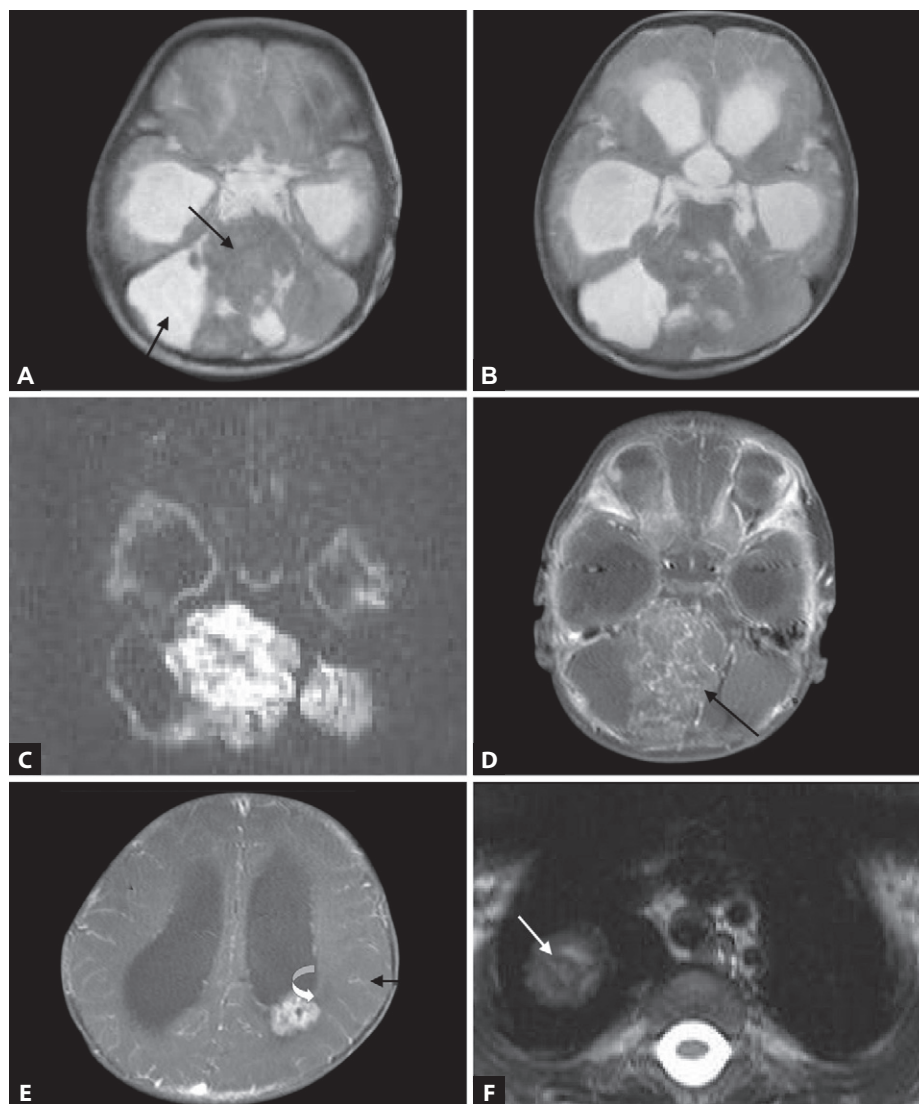
Figures 8A to F Atypical teratoid rhabdoid tumor (ATRT). (A and B) Axial T2-weighted images show a heterogeneous, solid, and cystic mass in the right cerebellar hemisphere with involvement of right cerebellopontine angle (arrows). Solid components of tumor are isointense to gray matter; (C) Diffusion weighted image shows decreased diffusion within solid components, consistent with high cell density; (D) Postcontrast images T1-weighted axial image show mild, heterogeneous enhancement throughout the solid portion of the tumor; (E) Enhancing lesion along ependymal lining of left lateral ventricle (curved white arrow) and leptomeningeal enhancement (black arrow) suggests tumor dissemination; (F) Well defined lesion in right apical region (white arrow) represents extracerebral metastasis, well described in this tumor
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

symptomatic tumors or as salvage procedure after radiotherapy and chemotherapy. Radiotherapy results in visual stabilization in majority of visual pathway gliomas which are not amenable or only partially amenable to surgery. Chemotherapy is used to delay if not to obviate the need of radiotherapy in children with progressive optic pathway gliomas.

In patients with mild symptoms, only observation is recommended, as the natural course of the disease is slow with no immediate threat to vision. Management of patients with NF type I include a careful neuroradiographic follow-up with a VEP every 3–6 months till 10 years of age. Treatment with chemotherapy is needed only if there is tumor progression and radiotherapy is generally avoided.

Dysembryoblastic Neuroepithelial Tumor

They are benign cortical tumors noted in older children or young adults. Their initial presentation is with intractable epilepsy. They were initially thought to be a form of cortical dysplasia, however, in spite of surgery some tumors have recurred, warranting continued surveillance following diagnosis and surgery **(Figs 10A and B)**.

Craniopharyngioma

Craniopharyngiomas **(Figs 11A to E)** are benign, partially cystic epithelial tumor usually arising in the sellar region from remnants of the Rathkes pouch. They are the most common nonglial brain tumors in children and commonly present in children between 5 years and 14 years. Craniopharyngiomas are classified
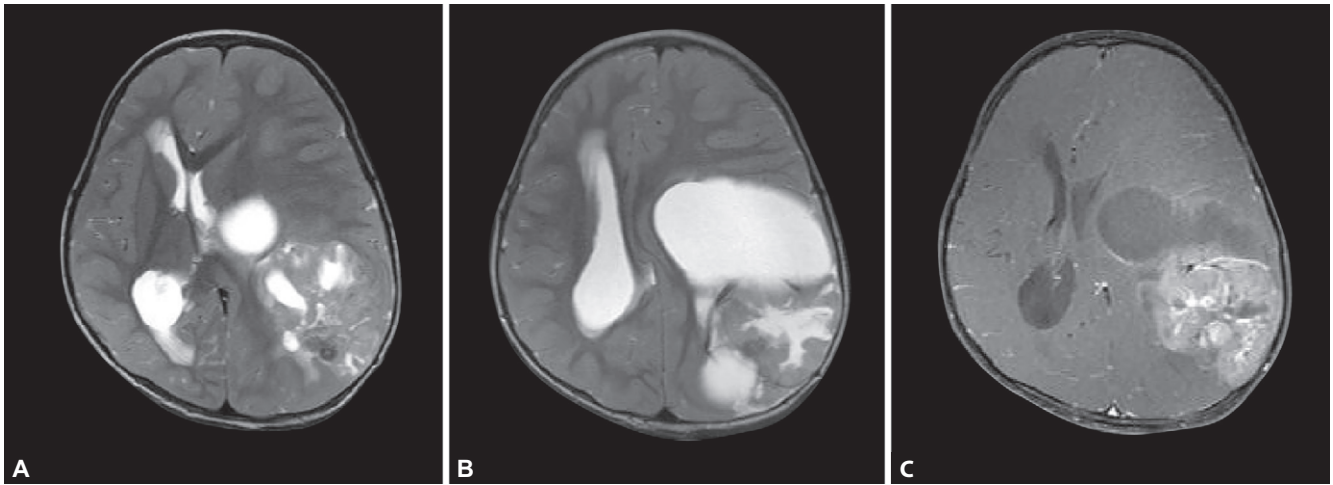
Figures 9A to C Supratentorial primitive neuroectodermal tumor (PNET). (A and B) A solid cystic mass with solid elements appearing isointense to cortex is seen on T2-weighted axial images. Note there is minimal perilesional edema; (C) Heterogeneous enhancement of solid component is seen on postcontrast axial image
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.
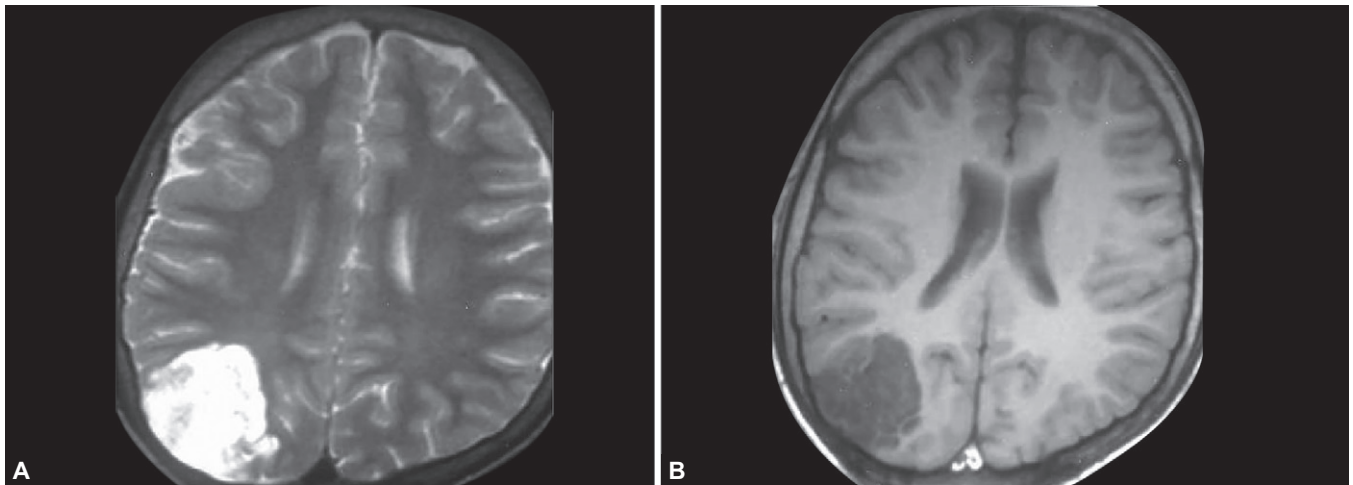
Figures 10A and B Dysembryoplastic neuroepithelial tumor (DNET). (A) T2-weighted axial image shows a well-defined, hyperintense cortically based wedge-shaped mass in right posterior parietal region. There is centripetal tapering toward the right lateral ventricle. No surrounding edema is seen; (B) The lesion appears hypointense on T1-weighted image. Note the cystic bubbly appearance of the tumor
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

anatomically based on their relative position to the optic chiasm or on the basis of their pathology (**Table 13**).

Clinical presentation and diagnosis Tumor growth characteristics vary considerably, which influences the clinical presentation. Visual and endocrine abnormalities are the most common symptoms at presentation. Symptoms may be the result of compression on the neural structures and/or obstruction of CSF causing increased intracranial pressure. The clinical symptoms can be classified according to the anatomical position of the tumor (**Table 14**).

Neuroimaging They are seen as well defined, lobulated heterogeneous masses, which almost always appear cystic on MRI and characteristically hyperintense on T1-weighted images due to cholesterol. Calcification is usually present.

Management and outcome The treatment of craniopharyngiomas involves surgical resection and radiotherapy. In completely resected tumors radiotherapy can be avoided. Radiation therapy

is however indicated in patients undergoing a subtotal resection. Endocrine abnormalities which may get exacerbated postsurgery needs meticulous management.

Choroid Plexus Tumors

These are CNS tumors usually seen in children less than 2 years of age and are basically intraventricular epithelial neoplasms arising from the choroid plexus in the lateral ventricle. Choroid plexus papillomas are known to be relatively benign, while choroid plexus carcinoma has metastatic potential and seeds into the CSF pathways. Immunopositivity for transthyretin (prealbumin) is useful in confirming the diagnosis of choroid plexus tumors. The tumors are associated with Li-Fraumeni syndrome and there has been a controversy regarding the relationship between simian virus 40 and development of choroid cell papillomas (**Figs 12A and B**).

Clinical presentation and management Choroid plexus papilloma is the most common among this group and presents with
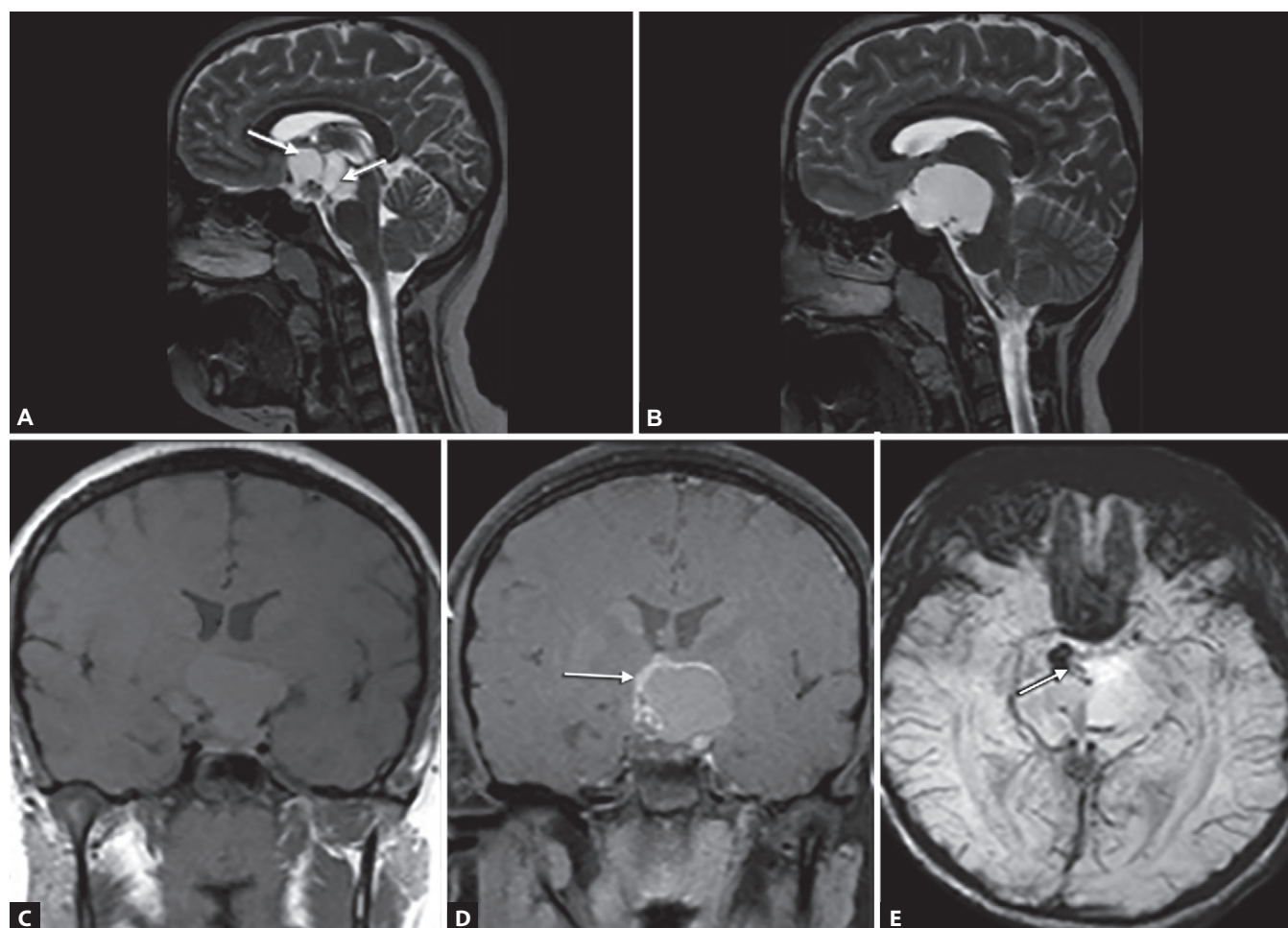
Figures 11A to E Craniopharyngioma. (A and B) Sagittal T2-weighted images showing a large lobulated septated cystic mass in suprasellar region (arrows); (C) T1W axial image showing hyperintense contents within the cyst; (D) Postcontrast image showing nodular enhancing rim (arrow); (E) Hypointense nodule is seen in lesion on SWI suggesting calcification (arrow)
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

Table 13 Classification of craniopharyngiomas

Anatomical	*Pathological*		
		Adamantous	*Papillary*
• Prechiasmatic	Age group	Children	Adults
• Retrochiasmatic	Location	Suprasellar	3rd ventricle
• Subchiasmatic	Appearance	Cystic	Solid
	Calcification	Common	Uncommon
	Recurrence	Common	Uncommon
			Mixed

Table 14 Clinical symptoms related to anatomical position of cranio-pharyngiomas

Tumor location	*Symptoms*
Prechiasmatic	• Optic atrophy • Decreased visual field acuity • Constriction of visual field
Retrochiasmatic	• Hydrocephalus • Papilledema • Compression of the optic tracts • Horizontal double vision
Subchiasmatic	• Endocrinopathy with panhypopituitarism (GH, TSH, ACTH, LH and FSH deficiency) and diabetes insipidus • Headaches

Abbreviations: GH, growth hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

macrocephaly and signs of increased intracranial pressure. Due to macrocephaly secondary to hydrocephalus, infants can present with head titubations, the *bobbly-head doll* syndrome.

The treatment of choice is total surgical resection which can be difficult in young infants. Radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinomas.

Germ Cell Tumors

They are predominantly tumors of midline structures of the pineal and suprasellar regions. The peak incidence is seen at 10–12 years. The analysis of alpha fetoprotein and beta-human chorionic gonadotropin are useful in establishing the diagnosis and monitoring treatment response. Up to 60% of pineal tumors are germinomas.

Clinical presentation and management They have a very insidious course and the initial presenting symptoms may be
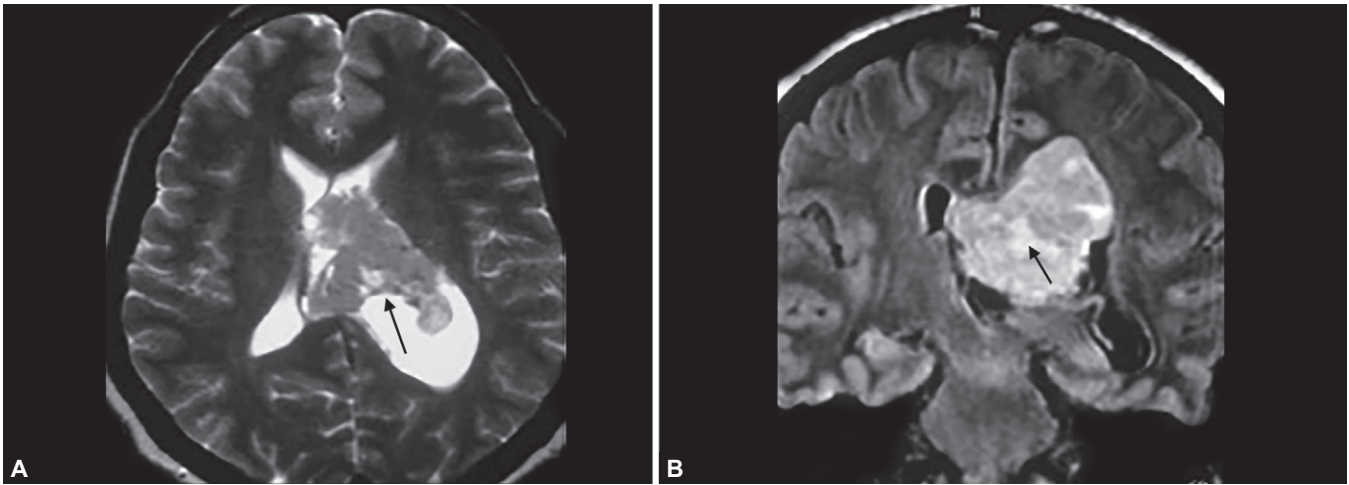
Figures 12A and B Choroid plexus papilloma (CPP). (A) Axial T2-weighted image; and (B) FLAIR coronal image shows a lobulated mass within the left lateral ventricle (arrow) with scattered hypointense flow voids indicating high vascularity (small arrow). Note the typical frond like appearance of these tumors. CPP cannot be differentiated from carcinoma by conventional imaging alone
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.
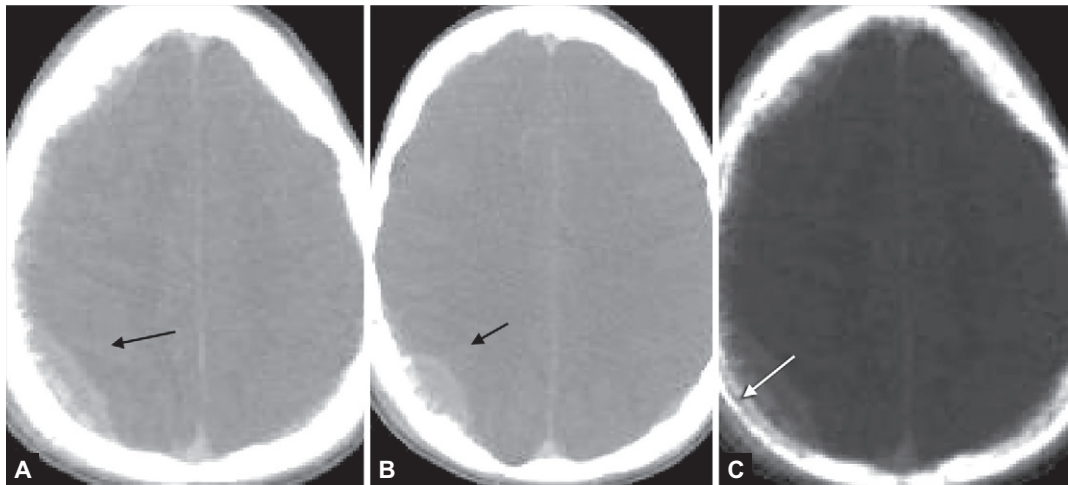
Figures 13A to C Metastasis from neuroblastoma. Noncontrast axial computed tomography (CT) of head showing isodense dural based extra-axial masses in parietal high frontoparietal region (arrows). Erosion of underlying bone with periosteal reaction seen on bone window (arrow in C)
Source: Dr SB Desai, Department of Radiology, Jaslok Hospital and Research Center, Mumbai, Maharashtra, India.

subtle, including dropping school performances and behavior issues.

Surgical biopsy is usually needed for diagnosis; however nongerminomatous germ cell tumors may be diagnosed on basis of protein marker elevation.

The postsurgical management of pure germinomas involves usage of chemotherapy and reduced dosage radiation. The approach to nongerminomatous germ cell tumors demands more aggression with more intense chemotherapy and craniospinal radiation.

Metastatic Tumors

Childhood acute lymphoblastic leukemias and non-Hodgkin lymphoma are seen to spread to the leptomeninges causing communicating hydrocephalus. Neuroblastomas, rhabdomyosarcomas, Ewings sarcoma, osteosarcoma and clear cell sarcoma of the kidney can metastasize to the brain parenchyma. Chloromas can occur throughout the neuroaxis. Medulloblastomas are the most common CNS tumor to metastasize extraneutrally **(Figs 13A to C)**.

IN A NUTSHELL

1. Central nervous system tumors are the second most common form of pediatric cancer.
2. The profile of pediatric brain tumors in India is similar to that reported globally with astrocytic tumors being the most common histological type.
3. A majority of pediatric brain tumors are infratentorial in location and primary brain and spine tumors outnumber the metastatic tumors in childhood.
4. Gross or near total excision of tumor is the single most important prognostic factor in deciding the outcome.
5. Survival rates have dramatically improved over the past century due to improved diagnostic investigations especially the MRI, along with skilled surgical techniques and radiotherapy.
6. Late effects can become evident over decades as the brain develops and can affect every body system; thus, needing long-term monitoring in survivors of brain tumors.

MORE ON THIS TOPIC

Aicardi J. Tumours of central nervous system and other space–occupying lesions. In: Aicardi J. Diseases of the Nervous System in Childhood. 3rd ed. MacKeith Press; 2009. pp. 501-47.

Barkowich AJ, Raybaud C. Pediatric Neuroimaging. 5th ed. Lippincott Williams and Wilkins; 2011.

Blaney SM, Haas-Kogan D, Poussaint TY, et al. Gliomas, ependymomas, and other non-embryonal tumors of CNS. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. USA: Lippincott Williams and Wilkins; 2011. pp. 717-808.

Brandão LA, Poussaint TY. Pediatric brain tumors. Neuroimaging Clin N Am. 2013;23:499-525.

Cage TA, Clark AJ, Aranda D, et al. A systematic review of treatment outcomes in pediatric patients with intracranial ependymomas. J Neurosurg Pediatr. 2013;11:673-81.

Chen YH, Gutmann DH. The molecular and cell biology of pediatric low-grade gliomas. Oncogene. 2014;33:2019-26.

Edmond JC. Pediatric brain tumors: the neuro-ophthalmic impact. Int Ophthalmol Clin. 2012;52:95-106.

Epelman S. The adolescent and young adult with cancer: state of the art—brain tumor. Curr Oncol Rep. 2013;15:308-16.

Fleming AJ, Chi SN. Brain tumors in children. Curr Probl Pediatr Adolesc Health Care. 2012;42:80-103.

Gerber NU, Mynarek M, von Hoff K, et al. Recent developments and current concepts in medulloblastoma. Cancer Treat Rev. 2014;40:356-65.

Harrington MH, Casella SJ. Pituitary tumors in childhood. Curr Opin Endocrinol Diabetes Obes. 2012;19:63-7.

Jain A, Sharma MC, Suri V, et al. Spectrum of pediatric brain tumors in India. Neurol India. 2011;59:208-11.

Khatua S, Sadighi ZS, Pearlman ML, et al. Brain tumors in children--current therapies and newer directions. Indian J Pediatr. 2012;79:922-7.

Manoranjan B, Provias JP. Congenital brain tumors: diagnostic pitfalls and therapeutic interventions. J Child Neurol. 2011;26:599-614.

Mohanty A. Spectrum of pediatric brain tumors in India. Neurol India. 2011;59:156.

Packer RJ, MacDonald TJ, Vezina G. Tumors of brain and spine. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Swaiman's Pediatric Neurology: Principles and Practice. 5th ed. USA: Elsevier; 2012. pp. 1339-87.

Chapter 45.11
Retinoblastoma
Anirban Das, Deepak Bansal

Retinoblastoma is a malignant tumor of the embryonic neural retina. It chiefly affects children below 5 years of age. It is caused by a sporadic or inherited mutation in the *RB1* tumor-suppressor gene. It can originate from single or multiple foci, in one or both eyes. In bilateral cases, it can arise in one eye, several months before being evident in the other. It is one of the most treatable childhood cancers, with survival rates exceeding 99% in the developed countries. However, 80% of the 8,000 children diagnosed annually with retinoblastoma, live in developing countries, among whom nearly 3,000 die of extraocular dissemination. Lack of awareness leads to delayed presentation. Treatment abandonment due to illiteracy, limited finances, as well as fear of enucleation remain major impediments.

Management of retinoblastoma requires a collaboration between several specialties, viz., (1) pediatrician, who should be able to identify early signs, including, leukocoria, motivate the family for therapy and refer to a tertiary care center; (2) ophthalmologist, who confirms the diagnosis, and provides surgical and focal treatments; (3) pediatric oncologist, who stages the disease, administers systemic chemotherapy and manages complications of treatment; (4) radiation oncologist, and (5) radiologist.

EPIDEMIOLOGY

Incidence

Retinoblastoma is the most common ocular malignancy in children and the most common solid tumor of childhood, after central nervous system (CNS) tumors and lymphomas. The Third National Cancer Survey in the United States reported an average incidence of 11 cases per million population in less than 5 years of age, or about 1:18,000 live-births. This rate has proven stable over time.

There is a 50-fold variation in global incidence of retinoblastoma. This is unique among pediatric malignancies, and provides opportunity for studying geographic and ethnic factors in disease pathogenesis. It is often felt that the incidence may be higher in developing countries, including Central and South America, the Middle-East and India. It is estimated that India has the highest number of affected children with retinoblastoma in the world. Data from the National Cancer Registry Project (1999–2000), Delhi, reported an incidence of 28 cases per million population in less than 5 years of age. High incidence is frequently reported from several African nations, where it accounts for 10–15% of cancers in children. It is widely perceived that retinoblastoma is more frequent among the lower socioeconomic stratum of society. While 250–350 new cases are detected in USA annually, the number in India could be as high as 1,200/year.

Age, Gender and Laterality

Retinoblastoma can present at birth. About 80% patients present below 4 years of age. Merely 5% present beyond 10 years. Nearly 60–75% cases have unilateral, while 25–40% have bilateral disease. The median age at diagnosis is 24 months for unilateral and 9–12 months for bilateral disease. Delayed presentation with advanced disease is a problem in the developing countries. In a study from the authors' center, the mean age of presentation of 72 children with retinoblastoma was 35 months, with a M:F ratio of 1.6:1.

Epidemiological Risk Factors

Potential associations include parental occupation (agriculture, metallurgy), advanced parental age, in-vitro fertilization, ultraviolet exposure, gestational exposure to radiation, low maternal education, poor antenatal care and prolonged exclusive breastfeeding beyond 6 months of age. Maternal micronutrient supplementation during pregnancy may be protective. Specific proteins synthesized by the human papilloma virus (HPV), SV40 and adenovirus are identified as capable of inactivating the retinoblastoma protein, suggesting an intriguing role for viral infections as a cofactor in pathogenesis. HPV was isolated from 70% of 76 and 26% of 39 eyes with nonfamilial retinoblastoma at Tata Memorial Center, Mumbai and PGIMER, Chandigarh, respectively. This link needs to be investigated for plausible vaccine-preventive strategies for retinoblastoma in developing countries.

ETIOPATHOGENESIS

Knudsons two-hit hypothesis, proposing that two events are required for tumor initiation, was based on the study of the retinoblastoma gene. *RB1* is a tumor-suppressor gene located on chromosome 13q14 that codes for a 110-kd protein (p110). p110 binds and inhibits the transcription factor E2F, thereby halting transcription of its target genes, which are responsible for cell-cycle progression. It also binds to histone deacetylase which results in silencing of transcription. Mutated or absent p110 results in uncontrolled cell proliferation. In both heritable and nonheritable retinoblastoma, biallelic mutations of the *RB1* initiate tumor growth. In heritable retinoblastoma, the first *RB1* mutation is constitutional, predisposing the child to retinal tumors. Though the loss of function of *RB1* causes genomic instability, it is still insufficient to cause retinoblastoma. The genomic instability probably leads to changes in other genes. The exact event that triggers malignant proliferation after mutation of *RB1* is unknown.

The tumor originates in the sensory retina and may grow into the vitreous cavity (endophytic) or, outwards into the subretinal space (exophytic) causing retinal detachment. A mixed pattern can occur. Diffuse infiltrating pattern with no obvious mass, or an extensive necrotic variant presenting with severe inflammatory reaction leading to pthisis bulbi, are well-known. Spontaneous regression due to complete occlusion of the central retinal artery can occur.

Microscopic examination reveals unifocal/multifocal tumor with mitotically active hyperchromatic cells, some differentiated to form Flexner-Wintersteiner (and less frequently Homer-Wright) rosettes, others simply forming pseudorosettes around blood vessels. Areas of coagulative necrosis and calcifications are common. Sometimes benign photoreceptor differentiation leads to the formation of fleurettes.

CLINICAL FEATURES

Retinoblastoma **(Figs 1 and 2)** frequently presents with the white-eye reflex (leukocoria). This results from either the tumor causing total retinal detachment, or being visible as a retrolental mass through the pupil. Vitreous hemorrhage can result in a dark red reflex (hemocoria), or black reflex (nigrocoria). Strabismus is the second most common complaint in the West. However, in developing countries, late presentation with buphthalmia and proptosis (often with a fungating mass) is frequent (~30% from India). In a study from Nigeria, proptosis with conjunctival chemosis was the most frequent presentation.

Retinoblastoma can present with rubeosis iridis (neovascularization of the iris), heterochromia iridis (secondary to neovascularization), hyphema (blood in the anterior chamber), glaucoma (secondary to neovascularization, or mechanical
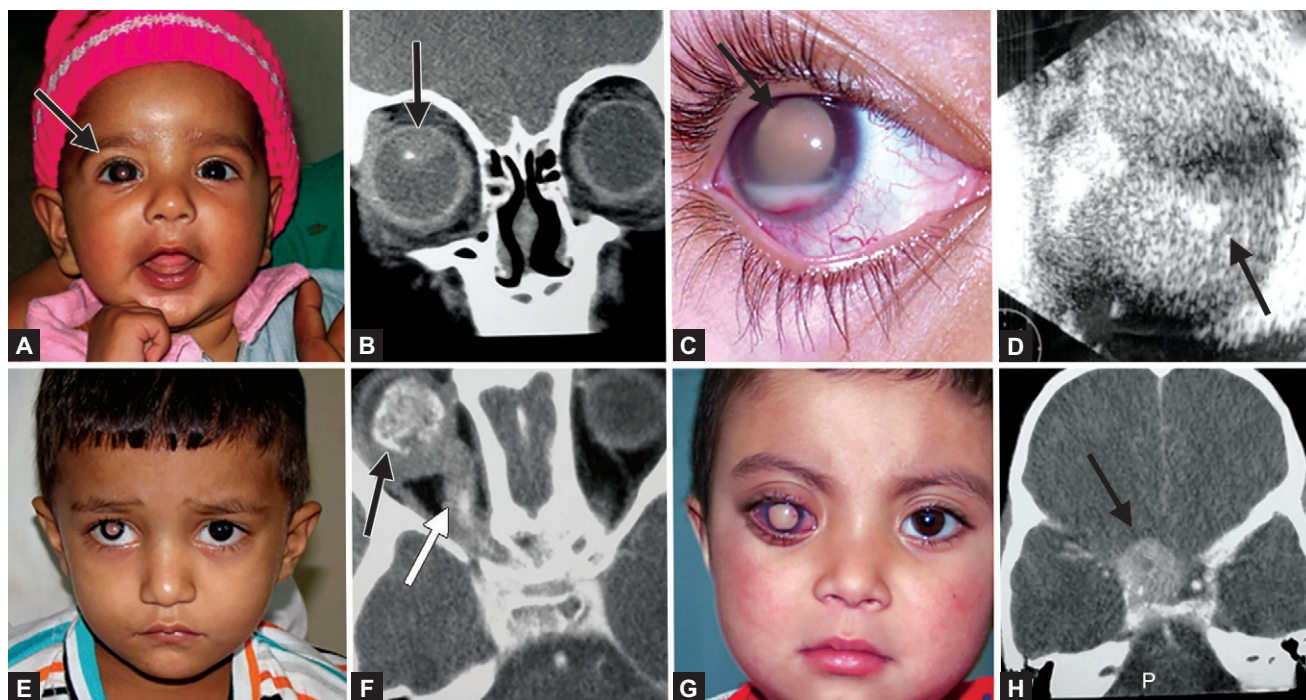
Figures 1A to H Myriad clinical manifestations of retinoblastoma. (A) Asymptomatic child with incidentally detected leukocoria in the right eye during a vaccination visit; (B) Computed tomography (CT) revealed intraocular mass (arrow) with white speck of calcification; (C) Presentation with leukocoria and tumor cells in the anterior chamber; (D) Ultrasonography demonstrating intraocular mass with specks of calcification (arrow); (E) A boy with the typical white-eye reflex in right eye; (F) CT revealed intraocular mass with calcification (black arrow) with thickened optic nerve (white arrow) suggestive of extraocular retinoblastoma; (G) Another patient with leukocoria in right eye; evaluation revealed group E disease in right eye and group B in left; (H) CT brain of patient in *G* demonstrated midline lesion (pineoblastoma), making it a case of trilateral retinoblastoma

Images C and D Source: Professor Usha Singh, Department of Ophthalmology, PGIMER, Chandigarh, India.

effect of the tumor) and aseptic orbital cellulitis. Retinoblastoma diffusely infiltrating into the retina can be clinically masquerade uveitis and endophthalmitis, resulting in delayed diagnosis.

In the West, 90% of children present with intraocular disease. However, in India, up to 35% present with locally advanced or metastatic disease. In Indonesia, this figure was as high as 73%. A similar scenario exists in Africa (Tanzania: 43%, Kenya: 60%, Congo: 90%). Metastatic disease can present with bone pain, scalp masses, preauricular and submandibular lymphadenopathy, seizures and raised intracranial tension.

Time from symptom-onset to treatment-initiation is about 8 weeks in the West. This duration is reported to be delayed to 8 months in India and 9–12 months in Africa. Causes of the delay include lack of awareness about the seriousness of the disease, fear of enucleation, lack of finances for travel and lack of timely referral by the primary physician. A delay exceeding 6 months from the first clinical sign to diagnosis is associated with 70% mortality. The contrasting scenario between the developed and the developing countries is summarized in **Table 1**.

Differential Diagnoses

Benign conditions (pseudoretinoblastomas) often simulate retinoblastoma **(Table 2)**.

APPROACH TO A PATIENT WITH SUSPECTED RETINOBLASTOMA

Clinical Approach

Typically, and in a contrast from conventional oncology practice, retinoblastoma is diagnosed on clinical and imaging evidence,

without a histological diagnosis. History is obtained with emphasis on antenatal (to exclude congenital cataract secondary to rubella), and perinatal events (to exclude retinopathy of prematurity), and family (to exclude hereditary disease) **(Fig. 3)**.

Clinical examination includes recording the visual acuity, slit-lamp (if possible) or indirect ophthalmoscopic examination. The anterior segment is examined to look for hyphema, rubeosis iridis, iris nodules, corneal edema, cataract, retrolental mass and retrolental fibroplasias to exclude pseudoretinoblastoma. The posterior segment is examined to note whether the mass is exophytic, endophytic or mixed, presence of retinal detachment and to exclude retrolental fibroplasia and Coats disease.

Examination under Anesthesia

A detailed evaluation of the entire retina, up to the ora serrata, in both eyes is needed. Intraocular pressure and corneal diameters should be measured. Retinal drawing and RetCam imaging, if available, should be performed. RetCam is a wide angle fundus camera, useful in accurately documenting retinoblastoma and monitoring response to therapy.

Imaging

Diagnosis is based on ultrasound or computed tomography (CT) demonstrating an intraocular mass with calcification. The detection of intraocular calcification is a key element to differentiate retinoblastoma from simulating lesions. Nearly 95% of retinoblastomas demonstrate calcification on histopathology. In children below 3 years of age, an intraocular calcified mass is most likely a retinoblastoma. However, in children older than 3 years of age, other intraocular lesions, such as retinopathy of prematurity,
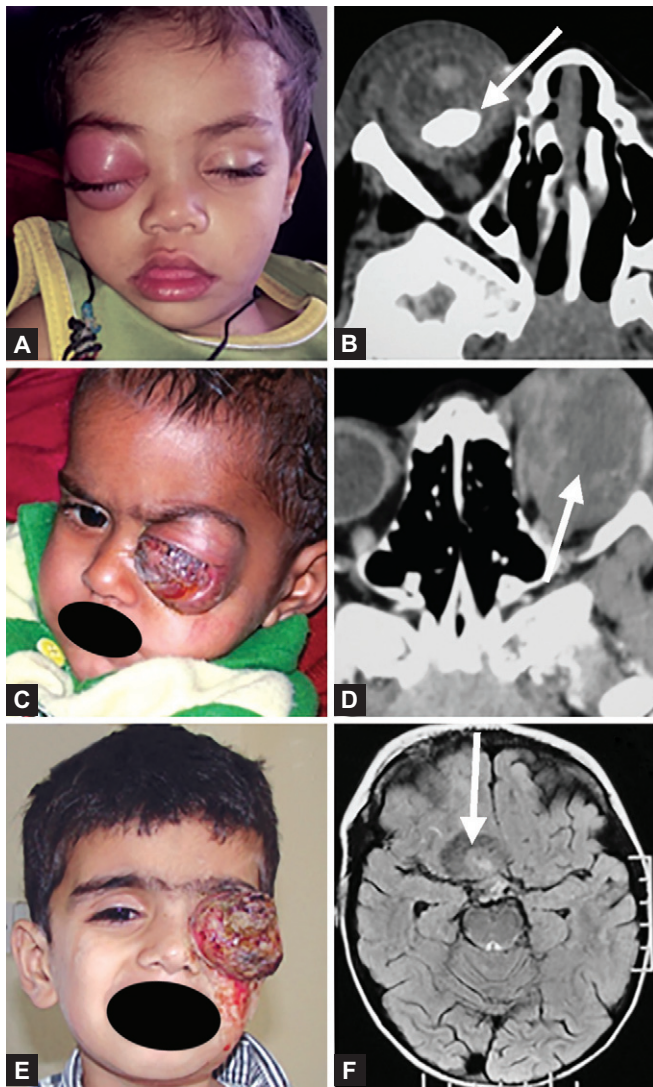
Figures 2A to F Late manifestations of retinoblastoma. (A) Child referred as orbital cellulitis and initiated on antibiotics; (B) Computed tomography (CT) revealed opacity in globe with calcification (arrow) suggestive of retinoblastoma; (C) Proptosis; (D) Large tumor filling the entire orbit; (E) Defaulted group E disease presenting with a large fungating mass, with (F) magnetic resonance imaging (MRI) demonstrating intracranial metastasis

Table 1 Contrasting state of retinoblastoma in the developed and developing world

	Developed countries	*Developing countries*
Incidence	Lower	Higher
Age of presentation	Earlier (often < 2 years)	Later (often > 2 years)
Duration: Symptom-onset to presentation	Shorter (~8 weeks)	Longer (often > 6 months)
Extent of disease	Majority intraocular	Majority extraocular
Medical and socioeconomic system	Better geared, developed society	Poverty, illiteracy, large families, lack of insurance. Limited awareness among health workers
Treatment compliance	Nearly 100%	50–60% abandon treatment
Decision making	Parents better empowered	Multiple opinions of family members, elders
Mortality	1%	Up to 70%

toxocariasis, Coats disease, retinal astrocytoma, and optic nerve drusen may appear as calcified masses. Magnetic resonance imaging (MRI) is more sensitive than CT for extraocular extension, including optic nerve thickening. In addition, MRI lacks radiation-exposure, desirable in retinoblastoma which has a predisposition to second malignancies. However, cost and availability of timely appointment is a limitation in developing countries.

Staging

The first step in staging is to determine whether the disease is intraocular or extraocular. Intraocular retinoblastoma is localized to the eye and may be confined to the retina or may extend to involve other structures, such as the choroid, ciliary body, anterior chamber, or optic nerve head. Extraocular retinoblastoma, as the name suggests is one in which disease has extended beyond the eyeball. It may be confined to the tissues around the eye (orbital retinoblastoma), or it may have spread to the central nervous system, bone marrow, or lymph nodes (metastatic retinoblastoma). The older Reese-Ellsworth staging system has been superseded by International Classification for Intraocular Retinoblastoma and the International Retinoblastoma Staging System for extraocular disease **(Tables 3 and 4; Fig. 4)**. Work-up for metastatic disease is

Table 2 Differential diagnoses of a child with leukocoria

S No.	*Disease*	*Etiology*	*Pathology*	*Differentiating features*
1.	Congenital cataract	Intrauterine infections, galactosemia, etc.	Opacification of the lens	USG: No mass
2.	Coats disease	Idiopathic	Subretinal fluid and lipid accumulation	Lipid exudation, no calcification
3.	Persistent hyperplastic vitreous	Developmental anomaly	Remnants of embryologic mesenchymal tissue in vitreous cavity	USG: Membranous echo from posterior surface of lens to disc
4.	Retinal detachment	Trauma, surgery, vascular disease	Fluid under the retina	USG: Hyper-reflective membranous echo attached to disc
5.	Retinopathy of prematurity	Postnatal oxygen therapy in preterm neonates	Abnormal retinal development	Fundus changes as seen by indirect ophthalmoscopy
6.	Toxocariasis	Infective	Chorioretinal scarring and vitreous inflammation, granulomas	Serology

Abbreviation: USG, ultrasonography.

Figure 3 Familial retinoblastoma. The father has a prosthesis in right eye (dashed white arrow). He had an enucleation at 2-year of age. His son presented with leukocoria in the left eye (white arrow) and was diagnosed to have retinoblastoma as well

Table 3 International classification for intraocular retinoblastoma

Group	Subgroup	Specific features
A	Small tumor	Size: ≤ 3 mm, location: > 1.5 mm from disc, > 3 mm from foveola
B	Larger tumor Macular Juxtapapillary Subretinal fluid	Size: > 3 mm Location: ≤ 3 mm to foveola Location: ≤ 1.5 mm to disc Clear subretinal fluid ≤ 3 mm from margin
C	Focal seeds C1 C2 C3	Discreet RBL with/without subretinal fluid < 1 quadrant, and Subretinal seeds ≤ 3 mm from tumor Vitreous seeds ≤ 3 mm from tumor Both subretinal and vitreous seeds ≤ 3 mm from tumor
D	Diffuse seeds D1 D2 D3	RBL with/without subretinal fluid ≥ 1 quadrant, and Subretinal seeds > 3 mm from tumor Vitreous seeds > 3 mm from tumor Both subretinal and vitreous seeds > 3 mm from tumor
E	Extensive	Size: > 50% of globe, or, touching lens, involving anterior segment, diffuse infiltrating tumor, tumor necrosis with aseptic orbital cellulitis, phthisis bulbi or opaque media from hemorrhage

Abbreviation: RBL, retinoblastoma.
Source: Linn MA. Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am. 2005;18:41-53.

generally indicated for patients with Group D disease and beyond, and includes: (1) lumbar puncture with cerebrospinal fluid (CSF) cytology, (2) bilateral bone marrow aspirate and trephine, (3) bone scan in symptomatic patients.

Table 4 International retinoblastoma staging system

Stage	Description
0	Patients treated conservatively
1	Eye enucleated, completely resected on histopathological examination
2	Eye enucleated, microscopic residual tumor
3	Regional extension a. Overt orbital disease b. Preauricular or cervical lymph node extension

4	Metastatic disease
	a. Hematological metastasis (without CNS involvement)
	   1. Single lesion
	   2. Multiple lesions
	b. CNS extension (with/without any other site of regional/metastatic disease)
	   1. Prechiasmatic lesion
	   2. CNS mass
	   3. Leptomeningeal and CSF disease

Abbreviations: CNS, central nervous system; CFS, cerebrospinal fluid.
Source: Chantada G, Doz F, Antoneli CB, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer.2006;47:801-5.

MANAGEMENT

The principles of management of retinoblastoma are summarized **(Tables 5 and 6; Fig. 5 and Flow chart 1)**:

- Primary aim is to save the child's life. Globe preservation and vision salvage are important, however, secondary aims.
- Treatment mandates collaborative planning involving pediatric oncologist, ophthalmologist and the radiotherapist for optimal outcome.
- Treatment planning in a developing country should take into account several factors, including surgical expertise, reliability of pathological examination, finances and compliance to follow-up.
- Treatment options include enucleation (removal of the eye), chemotherapy (delivered via intravenous, intra-arterial or intraocular routes), external beam radiation and a host of locally delivered (focal) treatments. Chemotherapy may be administered in adjuvant (following surgery) or neoadjuvant (before surgery) setting, depending on specific indications.

Management of Intraocular Retinoblastoma

Low-risk Intraocular Retinoblastoma (Stage 0 and Selected Stage 1)

Group A is treated by focal therapy alone. Groups B, C and D are frequently treated with 2–6 cycles of chemotherapy (consisting of vincristine, etoposide and carboplatin), along with focal therapy.

Intra-arterial chemotherapy Direct delivery of chemotherapy (melphalan alone, or in combination with carboplatin and topotecan) in the ophthalmic artery, accessed via cannulation of femoral artery, promises to be a paradigm-changer in the treatment of localized retinoblastoma. It may allow globe salvage by reducing tumor size and tumor-seed recurrence. Vision may be restored by reversal of retinal detachment, while avoiding the complications of radiotherapy and systemic chemotherapy. Adverse effects including vitreous hemorrhage and chorioretinal
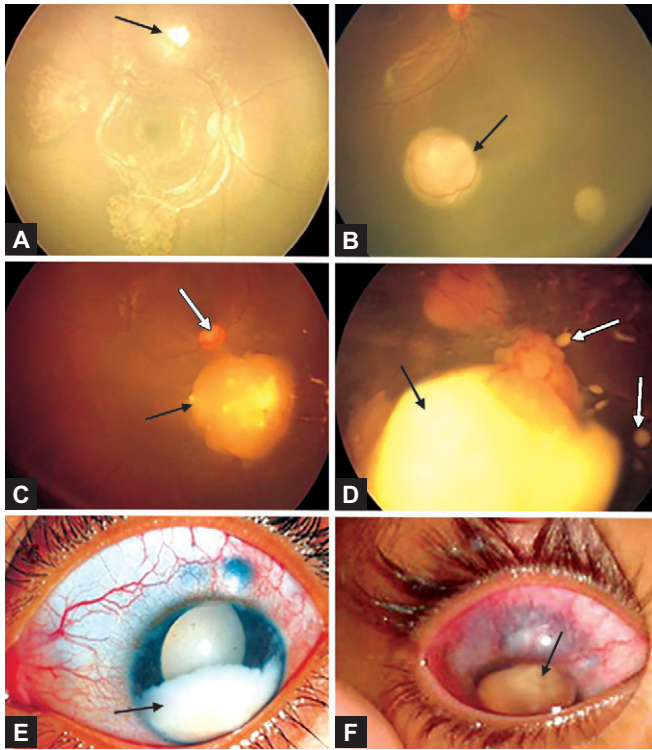
Figures 4A to F International classification for intraocular retinoblastoma. (A) RetCam imaging demonstrating group A disease with small lesion (arrow) away from the macula; (B) Group B disease with larger lesion (arrow) with subretinal fluid; (C) Group C disease (black arrow) with focal seeds (white arrow); (D) Group D disease (black arrow) with diffuse seeds (white arrows); (E) Tumor involving the anterior segment; (F) Tumor pushing the lens forward (arrow) and causing conjunctival congestion
Reproduced from ICMR National Guidelines in the Management of Retinoblastoma, 2010, with permission from Dr Vasantha Thavaraj.

atrophy are rare in expert hands. Prohibitive cost, lack of expertise, poor compliance to follow-up and the lack of potential benefit of systemic therapy in eradicating plausible occult metastases, are major impediments before it can be incorporated in regular practice in developing countries.

High-risk Intraocular Retinoblastoma

Unilateral group E and D disease with no visual potential undergo primary enucleation. Certain histopathological features in the enucleated eye are associated with a higher risk of local recurrence and/or systemic relapse and warrant adjuvant therapy with at least 6 cycles of chemotherapy. This subgroup of patients are said to have a *high-risk* disease. Two subgroups can be identified, viz.,

Enucleated with high-risk intraocular (extraretinal) disease (selected stage 1) The high-risk pathological features in this subgroup include invasion of any of the following: anterior chamber, iris, ciliary body, sclera, choroid or the optic nerve beyond the lamina cribrosa (resection-limit being free). Radiotherapy is not required. Cure rates exceed 90%.

Occasionally preoperative chemotherapy is indicated in group E patients: (1) To allow reduction in tumor size (e.g., buphthalmos or glaucoma), to enable safer surgery, (2) To buy time for the family to accept enucleation. This may lead to iatrogenic down-staging of the tumor and increases the chances of subsequent extraocular relapse. These patients should receive 6 cycles of chemotherapy, irrespective of high-risk histological features. Enucleation should be performed as soon as feasible, as delay is proven to increase risk of relapse.

Enucleated with microscopic residual disease (stage 2) Patients may have microscopic residual disease following enucleation. This includes tumor invasion through the resection-margin of the optic nerve, or trans-scleral invasion. The enucleation should be performed by an experienced ophthalmologist to obtain a long optic nerve stump (at least 10–15 mm). Cure rates vary between 70% and 80%. Treatment includes adjuvant chemotherapy (up to 12 cycles) and orbital radiotherapy.

Management of Extraocular Retinoblastoma

Patients presenting with Orbital and Locoregional Dissemination (Stage 3)

Presentation with overt extraocular disease is common in developing countries. Standard of care for stage 3 disease:
1. Preoperative chemotherapy
2. Enucleation
3. Orbital radiotherapy following enucleation, or at the end of chemotherapy, irrespective of the histopathological findings. Radiation to the involved preauricular and/or cervical lymph nodes is often recommended, though without adequate evidence
4. Adjuvant chemotherapy (To complete 12 cycles).

This multimodal treatment provides 60–85% chances of cure. Patients presenting with optic nerve involvement on imaging should be treated as stage 3 disease.

Patients with Metastatic Disease (Stage 4)

Until recently, metastatic disease was considered incurable. Children with CNS disease (stage 4b) have a limited chance of survival and best suited for palliative care. High-dose chemotherapy with autologous stem cell rescue may be efficacious in stage 4a patients. Low-dose chemotherapy and judicious use of orbital radiotherapy are often helpful for palliative care in children with poor prognosis.

Management of Bilateral Retinoblastoma

It is based on the status of the worse eye, and the visual potential of the better eye. Standard 3-drug protocol can be used (depending on the intraocular stage). The total number of cycles will depend upon the regression of the tumor as assessed periodically under anesthesia. At least 6 cycles are recommended. The eye that responds less well may need to be enucleated if there is no chance for useful vision. Radiation is better avoided in view of the higher incidence of germ-line mutations, predisposing these patients to secondary neoplasms. If indicated, lower dose radiotherapy (26–30 Gy) may be added as an adjuvant.

Management of Trilateral Retinoblastoma

It refers to bilateral retinoblastoma with neuroblastic tumor in the pineal gland or other midline structures. The reported incidence is 6% among bilateral tumors and 10% in those with a family history. The disease is highly fatal despite aggressive treatment.

Table 5 Different treatment modalities for retinoblastoma

Treatment modality	Indication	Comments	Complications
Focal therapies			
Laser photocoagulation	< 2 mm, posterior to equator	Argon green/diode infrared laser is used to completely cover each lesion	Iris burns and atrophy, lens opacity, vitreous hemorrhage, retinal traction, subretinal fluid, retinal holes and detachment
Thermotherapy	< 3 mm, posterior pole/mid-periphery, no vitreous seeding	Temperatures between 42° to 60°C are reached using infrared diode laser	
Cryotherapy	< 3 mm, < 1.5 mm thickness, equator/periphery	Ice crystals destroy tumor cells by rupturing cell membranes	
Enucleation			
Primary	Group E or D with no salvageable vision	Removal of entire globe with preservation of eye muscles; a minimum of 10 mm of optic nerve stump is essential	Generally safe; rarely hemorrhage and infection
Secondary	(1) Failure of conservative treatment, (2) Following neoadjuvant chemotherapy for stage 3		
Chemotherapy			
Neoadjuvant	Extraocular retinoblastoma	2–3 cycles followed by enucleation, radiation and adjuvant chemotherapy	Ototoxicity, myelo-suppression, neuropathy, seizures, dyselectrolytemia constipation, vomiting, hepatotoxicity, visual problems, pneumonitis
Adjuvant	Trans-scleral disease, involvement of cut-end of optic nerve, extraocular disease	Total 12 cycles of chemotherapy should be administered	
Chemoprophylaxis	Invasion of anterior chamber, iris, ciliary body, sclera, postlaminar optic nerve, massive choroidal involvement	6 cycles of chemotherapy should be administered to reduce the risk of relapse	
Periocular	Group C and D disease	Subtenon's injection of carboplatin	Cellulitis, fibrosis, dysmotility
Radiotherapy			
Plaque radiotherapy	≤ 15 mm in diameter, ≤ 7–8 mm thick, localized vitreous invasion over the tumor, peripheral tumors	Custom-made Iodine 126 or Ruthenium 106 plaques are surgically inserted and kept in situ for 3–4 days	Cataract, optic neuropathy, retinopathy, dry eye, muscle atrophy; second malignant tumors
External beam radiotherapy	Stage 2 and 3 disease, metastatic sites in stage 4	45 Gy is delivered to the target volume by 2 electron beams over 5 weeks	

Table 6 JOE: A common chemotherapy regimen for retinoblastoma

Drug	Dose (mg/m²)	Administration	Adverse effects
Vincristine	1.5	Intravenous push in a freshly inserted cannula	Constipation/ileus, peripheral neuropathy
Carboplatin	600	Dissolved in 5% dextrose (minimal dilution 500 µg/mL), infused over 1 hour	Ototoxicity, myelosuppression, peripheral neuropathy, electrolyte imbalance, vomiting
Etoposide	300	Dissolved in 0.9% saline (maximum concentration of 0.4 mg/mL), infused over 4 hours	Myelosuppression, seizures, hepatotoxicity, visual problems, pneumonitis

Dose-modification for children < 10 kg: 50% for < 6 months, 75% for 6–12 months, 100% for > 12 months. Each course is administered at 21 days intervals, once neutrophils are ≥ 1 × 10⁹/L and platelets ≥ 100 × 10⁹/L. The chemotherapy can be easily administered on a daycare basis. Ensure adequate antiemesis.

Psychosocial Aspects of Treatment

Retinoblastoma is a highly curable cancer. Unfortunately, outcomes are far worse in developing countries because of delayed presentation with advanced disease and treatment abandonment (50–60%). Community awareness programs are important, and have been documented to halve the incidence of extraocular disease in Saudi Arabia and Honduras. Measures to prevent treatment abandonment include: (1) repetitive counseling of the family to accept enucleation, where indicated, (2) emphasizing that a near-normal lifestyle can be achieved with one eye (normal depth of vision, albeit with some loss of field of vision), and (3) use of primary orbital implant to rehabilitate the child with a life-like prosthetic eye.

Follow-up

The periodicity of follow-up is 3-monthly examinations for the first year, 4-monthly during the second year, 6-monthly in the 3rd year and yearly thereafter, till the age of 10 years. Majority of recurrences occur within 3 years of diagnosis and are extremely rare after 5-years of age. Each follow-up visit should include:

- Examination of the diseased eye if treated conservatively, as well as the fellow eye.
- Examination of the ophthalmic socket in enucleated patients: Palpation should be done after the artificial shell is removed.
- Physical examination to exclude metastatic disease.
- Monitoring for secondary malignant neoplasms. These are more frequent in patients with germ-line mutations (4% at a mean follow-up of 11 years, cumulative mortality of 22.5% at 50 years of age), as well as following external beam radiotherapy. Osteosarcoma is the most common **(Fig. 6)**; however other sarcomas, ocular melanomas, leukemias, etc., have been reported.
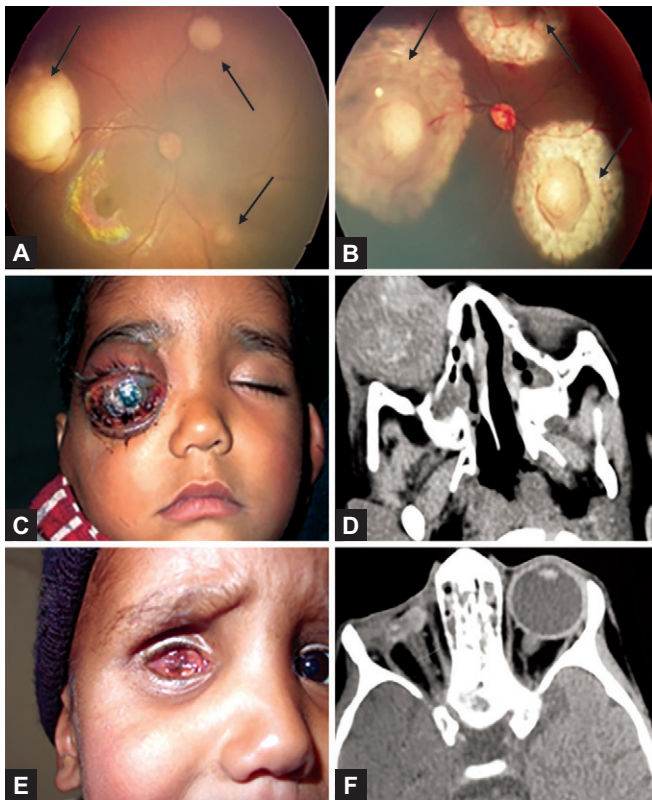
Figures 5A to F Response to treatment. (A) Multifocal group B disease with 3 lesions; (B) Following treatment with laser photocoagulation; (C) and (D) Extraocular disease, (E) and (F) Following chemotherapy and enucleation
Source: Professor Usha Singh, Department of Ophthalmology, PGIMER, Chandigarh, India.

• Screening for trilateral retinoblastoma is recommended in patients with bilateral disease, particularly those diagnosed in infancy and in those with a positive family history. MRI (or CT) is recommended every 6-month till 5 years of age.

PREVENTION

Genetic testing for *RB1* is the standard of care in developed countries. *RB1* mutations are inherited in an autosomal dominant fashion. Penetrance is high at 90–95%. Molecular testing of DNA from the proband's white blood cells (or other nontumorous cells), as well as from the tumor, may detect the cancer-predisposing *RB1* mutation. If a cancer-predisposing *RB1* mutation is identified, mutation analysis can clarify the genetic status of at-risk sibs and offspring. If not available or uninformative, indirect testing using linkage analysis can be used in familial retinoblastoma. Empiric recurrence risk estimates are useful when molecular genetic testing of *RB1* and linkage analyses are unavailable **(Table 7)**.

Prenatal testing is possible if the heritable *RB1* mutation in the parent is known or if *RB1* linkage analysis is informative in the family. If the fetus carries the *RB1* mutant allele present in the family, it is recommended that early delivery at 36 weeks gestation be performed. This will allow the earliest detection of visually threatening tumors at a time when they can still be treated with minimally invasive therapies to achieve potential good vision. Retinoblastomas grow rapidly around the time of birth, and every day can make a difference in the ultimate outcome.

Timely molecular diagnosis of *RB1* mutations enables earlier treatment, lower risk, and better health outcomes for patients with retinoblastoma. It empowers families to make informed family-planning decisions and costs less than conventional surveillance. Preimplantation genetic diagnosis may be an option for families in whom the disease-causing mutations have been identified.

Flow chart 1 Management of unilateral retinoblastoma
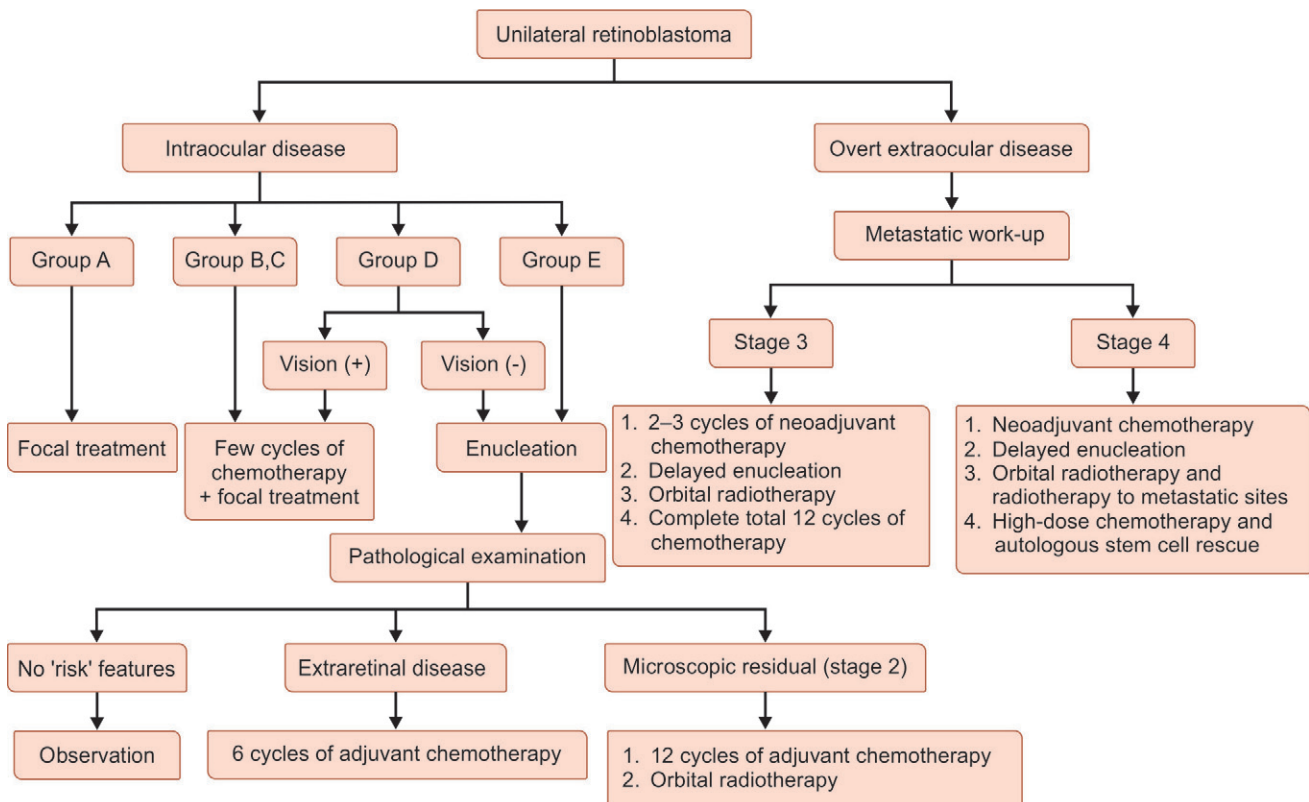
Figure 6 Second malignancy in a child treated for retinoblastoma. The child underwent enucleation of left eye for group E disease at 2 years of age and presented at 9 years with osteosarcoma of the right humerus

Table 7 Empirical risk of developing retinoblastoma in family members of an index patient

Disease category	Risk of developing retinoblastoma in:		
	Subsequent pregnancy (sibling)	Offspring of affected parent (progeny)	Offspring of normal sibling of affected patient
Family history present			
Unilateral/bilateral	40%	40%	7%
No family history			
Unilateral	1%	8%	1%
Bilateral	6%	40%	1%

Adapted from: Friedman DL. Retinoblastoma. In: Lanzkowsky P. Manual of pediatric hematology and Oncology. 5th ed. London: Academic Press; 2011. pp. 761-2.

IN A NUTSHELL

1. Retinoblastoma is the most common intraocular malignancy of childhood.
2. White-eye reflex is a young child is the most frequent manifestation.
3. Unilateral disease is frequent (60–75%), presents between 2 and 3 years of age, and is usually nonhereditary and unifocal.
4. Bilateral disease (25–40%) presents between 6 and 18 months of age and is more likely to be multifocal. It is presumed that these patients have the hereditary form of the disease, even in the absence of a positive family history.
5. Nonmetastatic retinoblastoma is highly curable with multi-modality treatment (including enucleation, chemotherapy, focal therapies and radiation), with cure rates exceeding 95% in the West.
6. Delayed presentation with advanced disease (proptosis) and metastases to the CNS, bone and marrow is common in developing countries.
7. Awareness and early diagnosis is the key to saving life and/or vision. Life has priority over vision in treatment.
8. The pediatrician plays an important role in early identification, appropriate referral, encouraging treatment, allaying fears, supporting enucleation (if indicated) and encouraging compliance to treatment and follow-up.

MORE ON THIS TOPIC

Bansal D. Brainstorming–management of unilateral Group E retinoblastoma. PHO Bulletin. 2013;5:8-14.

Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries: Impact of socioeconomic and health-related indicators. Br J Ophthalmol. 2010;94:1432-6.

Galluzzi P, Hadjistilianou T, Cerase A, et al. Is CT still useful in the study protocol of retinoblastoma? Am J Neuroradiol. 2009;30:1760-5.

Hurwitz RL, Shields CL, Shields JA, et al. Retinoblastoma. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2011. pp. 809-34.

Kumar A, Moulik NR, Mishra RK, Kumar D. Causes, outcome and prevention of abandonment in retinoblastoma in India. Pediatr Blood Cancer. 2013;60:771-5.

Meel R, Radhakrishnan V, Bakhshi S. Current therapy and recent advances in the management of retinoblastoma. Indian J Med Paediatr Oncol. 2012;33:80-8.

National Guidelines in the Management of Retinoblastoma. New Delhi: ICMR; 2010.

Rodriguez-Galindo C, Wilson MW. Retinoblastoma. New York: Springer; 2010.

Chapter 45.12
Soft Tissue Tumors
Sandeep Jain, Gauri Kapoor

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant disorders originating from primitive mesenchymal cells. These may arise from muscle, connective tissue, supportive tissue or vascular tissue. Nearly half of the STS are constituted by rhabdomyosarcoma (RMSs) and the rest are classified as nonrhabdomyosarcoma soft tissue sarcoma (NRSTS). They initially present as asymptomatic solid masses, or may be symptomatic due to pressure symptoms or invasion of adjacent structures. As a group, these are locally invasive tumors with high propensity for metastasis and need multidisciplinary care involving a team of pediatric oncologist, surgeon and radiation specialist. In infancy and early childhood, some NRSTS may behave in a benign fashion with excellent outcome with surgery alone. With current multimodality treatment, outcome of nonmetastatic disease has improved significantly in last two decades. Therefore, the family physician/pediatrician should be aware of common presentations of this rare tumor and facilitate early diagnosis ensuring referral to specialized pediatric cancer units. This chapter reviews the information regarding the epidemiology, genetics, diagnosis, treatment, and prognosis of childhood RMS and NRSTS.

EPIDEMIOLOGY

Rhabdomyosarcoma is the most common malignant soft tissue tumor of childhood accounting for 3% of all malignancies as reported by Indian Council of Medical Research. In the United States, it accounts for approximately 350 new cases each year in children up to 19 years of age. There is a slight male predominance with a male: female ratio of 1.4:1. There are two age peaks: (1) 2–6 years and (2) 15–19 years. Though most of the cases occur sporadically, the development of RMS has been associated with certain familial syndromes, such as neurofibromatosis, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome and Costello syndrome. Maternal and paternal use of marijuana or cocaine and first-trimester prenatal X-ray exposure is postulated as potential environmental trigger.

As a group, NRSTS account for 2–3% of cancers in children less than 15 years of age and 6% of cancers in 15–19-year-old patients. Although the majority of NRSTSs are sporadic, certain predisposing factors are known to account for a subset of these tumors. Genetic predispositions such as familial p53 mutations (Li-Fraumeni syndrome), familial retinoblastoma, and neurofibromatosis are known to increase the lifetime risk for NRSTS. There is no published data in regard to incidence of childhood soft tissue sarcomas from India. However, they form approximately 4% of all childhood cancer patients seen at the Tata Memorial Hospital, Mumbai, Maharashtra, India compared to 7% in USA.

PATHOLOGY AND MOLECULAR BIOLOGY

Rhabdomyosarcoma is a differential diagnosis of small round blue-cell tumors of childhood with typical identification of cross-striation characteristic of skeletal muscle or rhabdomyoblasts. International Classification of Rhabdomyosarcoma categorizes RMS in three broad subtypes: (1) embryonal, (2) alveolar, and (3) undifferentiated **(Table 1)**. Under this classification, the presence of any alveolar component is sufficient to categorize the tumor as an alveolar subtype and, therefore, unfavorable. Immunohistochemical staining is an important adjunct to identifying muscle specific proteins and confirming the suspected diagnosis of RMS. These proteins include muscle specific actin and myosin, desmin, myoglobin, Z-band protein, and Myo D.

The NRSTSs are a very heterogeneous group of sarcomas that are classified as per the World Health Organization system,

Table 1 Histological subtype and associated genetic abnormality in rhabdomyosarcoma (RMS)

Histological subtypes	Prevalence	Genetic abnormality	Prognosis
Embryonal RMS Spindle variant/ Botryoid variant	65%	Loss of heterozygosity at the 11p15.5 locus and gains of chromosome 8	Intermediate Good
Alveolar	20%	t(2;13)(q35;q14) 59% (PAX3–FOX 01) t(1;13)(q36;q14) 19% (PAX7–FOX 01	Poor
Undifferentiated	15%		Poor

Table 2 List of nonrhabdomyosarcoma soft tissue sarcomas in children

Types	Chromosomal aberration
Synovial sarcoma	t(X;18)(p11.2;q11.2)
Infantile fibrosarcoma	t(12;15)(p13;q26); trisomy 8, 11, 17, 20
Peripheral neuroectodermal tumor	t(11;22)(q24;q12); t(21;22) (q12;q12)
Malignant fibrous histiocytoma	Complex abnormalities
Leiomyosarcoma	Deletion of 1p Other complex abnormalities
Neurogenic tumors: Malignant schwannoma Neurofibrosarcoma Malignant peripheral nerve sheath tumor	Complex abnormalities
Rare tumors: Alveolar soft-part sarcoma Angiosarcoma Hemangiopericytoma Clear cell sarcoma Epitheloid sarcoma Desmoplastic small round cell tumor Extraskeletal chondrosarcoma	t(X;17)(p11.2;q25) t(12;19),t(13;22) t(12;22)(q13;q12); t(2;22)(q33;q12); Inactivation of SMARCB1 t(11;22)(p13;q12) t(9;22)(q22;q12); t(9;17)(q22;q11)

using lines of differentiation in order to categorize them into adipocytic, fibroblastic/myofibroblastic, fibrohistiocytic, smooth muscle, pericytic (perivascular), and vascular types, as well as tumors of uncertain differentiation. Characteristic chromosomal translocations have been identified in specific subgroups of NRSTSs and are cornerstone for the diagnosis of these tumors, especially in cases where in the pathological evaluation is inconclusive. Various common and rare NRSTS and their associated chromosomal aberrations are listed in **Table 2**.

CLINICAL FEATURES

Rhabdomyosarcoma may occur in any anatomic location of the body where there is skeletal muscle, as well as in sites where no skeletal muscle is found (e.g., urinary bladder, common bile duct). Initial symptoms may be progressive painless lump or associated pressure symptoms on adjacent organs, nerves, muscles, or blood vessels.

Head and neck is the most common site accounting for 40% of all RMS. Half of these arise in parameningeal sites (often referred to as *skull base*); and one-fourth each arise from orbital and nonorbital, nonparameningeal locations such as the scalp, face, buccal mucosa, oropharynx, larynx, and neck. Orbital site has the best prognosis owing to its early presentation and lack of lymphatics while parameningeal location is considered an unfavorable site because

of inability to achieve complete surgical resection. Orbital tumors present with unilateral proptosis, chemosis, impaired mobility, ptosis, and lid or conjunctival mass. Symptoms from a parameningeal primary tumor include cranial nerve palsy, facial pain and swelling, meningeal irritation, nasal voice, mouth breathing, trismus, and painless adenopathy. Parameningeal primary tumors may erode skull-base bone, invade the dura or brain.

The second most frequent primary site is genitourinary accounting for 25% of all RMS, divided almost equally between bladder and prostate (unfavorable site) and other genitourinary sites (female genital tract and paratesticular). Bladder tumors tend to grow intraluminally, in or near the trigone, and may present as hematuria, urinary obstruction, and occasionally the extrusion of mucosanguineous tissue. Prostate tumors usually produce large pelvic masses with or without urethral strangury; constipation may occur. Sarcoma botryoides may protrude from the vagina with or without bleeding. Paratesticular tumors usually present as painless mass.

Next in frequency are extremity lesions (20%), which present with an enlarging, usually painless mass, more commonly occurring in adolescents with alveolar histology. The remaining 15% of tumors are distributed among several sites including thorax, trunk, and intra-abdominal (including retroperitoneum). The history is usually of silent growth and presentation of a large mass associated with obstructive symptoms. **Figures 1A to C** show three frequent sites of RMS in children less than 10 years of age.

The NRSTSs usually present as isolated soft tissue masses; symptoms such as pain or numbness may occur due to local invasion of adjacent structures. The most common sites for NRSTSs are the extremities, followed by the trunk and abdominal regions, thorax, and head and neck area. These tumors can often be slow growing; therefore, a high index of suspicion is important for early recognition.

APPROACH TO DIAGNOSIS

Differential diagnosis, therefore, depends on the location and symptoms and physicians need to have a high index of suspicion to make an early diagnosis. When a suspicious lesion is detected it is important to do a complete work-up and biopsy of the lesion. Initial assessment should include complete history and physical examination including measurements of the primary tumor and assessment of regional lymph nodes. This is usually followed by imaging that is aimed at delineating the extent of primary disease, followed by biopsy for confirming the diagnosis histologically and then the staging work-up. The primary tumor is assessed by magnetic resonance imaging (MRI) or computed tomography (CT) scan depending on the site. For orbital and parameningeal primary sites, the MRI should include the brain to characterize intracranial

extension. For purpose of staging CT chest is done and bone marrow aspirate and biopsy for patients with RMS. Additionally, cystoscopy may be required for genitourinary presentations, and direct nasopharyngoscopy and laryngoscopy for upper airway primary tumors. Complete blood count and a standard chemistry including liver and kidney function are done.

In patients with limited primary disease, the surgeon aims at wide local excision to achieve negative margins, and in all other cases only biopsy is indicated without compromising the integrity of vital organs. In extremity and head and neck tumors, biopsy of draining lymph nodes and in older children (> 10 years) with paratesticular tumor, ipsilateral retroperitoneal lymph node dissection is also recommended.

Two major staging systems are currently employed in combination: the Children's Cancer Group (CCG) surgico-pathologic staging system (CGSS) developed by the Intergroup Rhabdomyosarcoma Study Group (IRSG) in 1972 **(Table 3)**, and the pretreatment, site-modified tumor node metastasis (TNM) staging system (stage), developed by the IRSG **(Table 4)**. The TNM system, divides patients into favorable and unfavorable depending on site, size and nodal involvement.

For NRSTS, CT or MRI are essential radiographic studies to evaluate tumor extent, pattern of infiltration, and status of adjacent structures to allow surgical and radiation planning of treatment. To complete staging evaluation, thoracic CT scanning is generally recommended as chest is the most frequent site of distant metastasis. The NRSTSs are generally staged using American Joint Committee on Cancer Staging system which incorporates tumor size (T1 ≤ 5 cm, T2 > 5 cm) and depth (a-superficial, b-deep), nodal involvement (N), distant metastases (M), and histologic grade (G) as shown in **Table 5**.

MANAGEMENT OF RHABDOMYOSARCOMA

All children with RMS require systemic chemotherapy along with surgery or radiotherapy or both, for providing local control. Therefore, if possible it is preferred if patients are referred to institutions with staff that have adequate experience in treating pediatric tumors and have facility to provide multidisciplinary care. The sequence and timing of these modalities have to be planned and executed with regard to the patient's age, site of tumor, risk stratification and the late effects of treatment.

Chemotherapy

Rhabdomyosarcoma is a chemosensitive tumor and chemotherapy is the backbone of treatment. This is because all patients with apparently localized disease are believed to have occult metastatic spread. The most effective chemotherapeutic agents are vincristine,
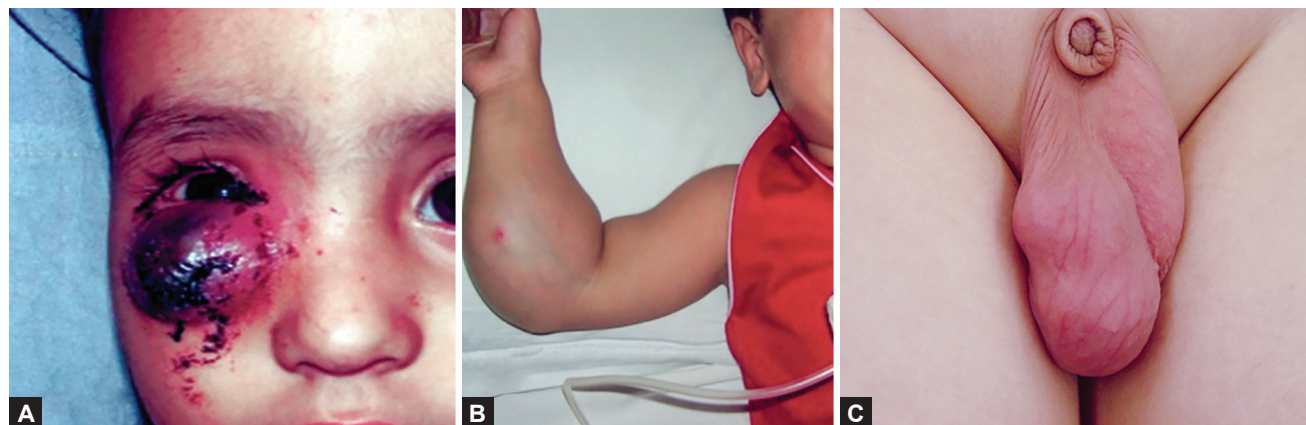
Figures 1A to C (A) 5-year-old child with right lower eyelid mass; (B) 3-year-old child with right forearm mass; (C) 9-year-old child with right paratesticular mass

Table 3 Clinical group staging system employed in intergroup rhabdomyosarcoma studies I–III

Clinical group	Extent of disease and surgical result
IA	Localized tumor, confined to site of origin, completely resected
B	Localized tumor, infiltrating beyond the site of origin, completely resected
IIA	Localized tumor, gross total resection, but with microscopic residual disease
B	Locally extensive tumor (spread to regional lymph nodes), completely resected
C	Extensive tumor (spread to regional lymph nodes), gross total resection, but with microscopic residual disease
IIIA	Localized or locally extensive tumor, gross residual disease after biopsy only
B	Localized or locally extensive tumor, gross residual disease after major resection (≥ 50% debulking)
IV	Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor

Table 4 Tumor node metastasis (TNM) staging of rhabdomyosarcoma: TNM pretreatment staging classification (intergroup rhabdomyosarcoma studies [IRS] IV)

Stage	Sites	T-invasiveness	T-size	N	M
I	Orbit	T1 or T2	a or b	N0 N1 or Nx	M0
	Head and neck[a]	T1 or T2	a or b	N0 N1 or Nx	
	Genitourinary[b]	T1 or T2	a or b	N0 N1 or Nx	
II	Bladder/prostate	T1 or T2	a	N0 or Nx	M0
	Extremity	T1 or T2	a	N0 or Nx	
	Cranial parameningeal	T1 or T2	a	N0 or Nx	
	Other[c]	T1 or T2	a	N0 or Nx	
III	Bladder/prostate	T1 or T2	a	N1	M0
	Extremity	T1 or T2	b	N0 N1 or Nx	
	Cranial parameningeal	T1 or T2	b	N0 N1 or Nx	
	Other[c]	T1 or T2	b	N0 N1 or Nx	
IV	All	T1 or T2	a or b	N0 or Nx	M1

T (tumor): T1, confined to anatomic site of origin; T2, extension; [a] ≤ 5 cm in diameter; [b] > 5 cm in diameter.
N (regional nodes): N0, not clinically involved; N1, clinically involved; Nx, clinical status unknown.
M (metastases): M0, no distant metastases; M1, distant metastasis present.
[a] Excluding parameningeal; [b] Nonbladder-nonprostate; [c] includes trunk, retroperitoneum, etc.

Table 5 The American Joint Committee on Cancer (AJCC) staging for soft tissue sarcoma

Stage	Size	Nodal status	Metastasis	Grade
Stage IA	T1a	N0	M0	G1
	T1b	N0	M0	G1
Stage IB	T2a	N0	M0	G1
	T2b	N0	M0	G1
Stage IIA	T1a	N0	M0	G2
	T1b	N0	M0	G2, 3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

T1 is defined as tumor less than or equal to 5 cm in greatest length with T2 greater than 5 cm. The *a* designated a superficial tumor as located exclusively above the superficial fascia without invasion of the fascia; *b* designates a deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. N1 and M1 are positive findings for nodal or distant metastatic spread. The G designates a grade on a three-point scale G1 well differentiation; G2 moderate differentiation, G3 poor or undifferentiation.

advantages in terms of myelotoxicity and gonadal toxicity but is associated with a higher risk of renal toxicity. However, there is no concrete evidence to recommend superiority of either alkylating agent over the other. Currently, the VAC regimen is considered the mainstay of chemotherapy in IRS trials whereas the IVA regimen (ifosfamide, vincristine, and actinomycin D) is considered the gold standard in Europe. Patients with metastatic disease continue to have poor outcome and increasing the dose of alkylating agent has not translated in survival benefit. Because of unsatisfactory results among high-risk patients, other agents such as topotecan, irinotecan and doxorubicin have been tested in various trials, however, none of them have shown superior results compared to conventional VAC regimen and novel strategies are required.

Radiotherapy

Radiotherapy (RT) is an effective modality of treatment for achieving local control in RMS patients with microscopic or gross residual disease. These are moderately radiation-sensitive tumors and RT is recommended for all patients except those with embryonal histology that where tumor was completely excised initially with negative margins. RT is administered at week 9 or 12 except for the patients with parameningeal disease with intracranial extension, bony erosions or neurological deficits, where in RT may be started upfront or earlier with concurrent chemotherapy. The dose of radiation depends on the amount of residual disease after surgery and ranges from 36 Gy to 50 Gy. It is administered once per day, 5 days a week, 1.8 Gy per fraction, to a total of 50.4 Gy. The treatment volume is determined by the extent of tumor at diagnosis prior to surgical resection with an appropriate margin which may be influenced by the surrounding normal tissue structures. If there is lymph nodal involvement, these regions are treated in contiguity with the primary tumor.

Surgery

At initial presentation primary en bloc resection should be performed only if complete resection is possible (i.e., with histologically detected-free margins) and the excision is nonmutilating. If this is not possible, a biopsy is recommended and surgical resection is then attempted after induction chemotherapy (4 cycles). Regional nodal exploration, possibly with sentinel node mapping, is recommended in extremity lesions. In children, older

actinomycin D, and cyclophosphamide (VAC). This regimen has been pioneered in North America and is typically given every 3 weeks for a total of 8–10 months. The initial four cycles are termed as induction or neoadjuvant chemotherapy. Patients are re-evaluated at 9–12 weeks (after 4–5 cycles) and local therapy is then given in the form of surgery or radiotherapy or both. During radiotherapy lower doses of chemotherapy are continued depending on the protocol. Adjuvant chemotherapy is resumed after completion of local therapy for 8–10 additional cycles with similar chemotherapeutic agents to complete 8–10 months. Patients with low-risk rhabdomyosarcoma with very favorable characteristics may receive VA without cyclophosphamide. European protocols prefer ifosfamide over cyclophosphamide as it offers some

than 10 years with paratesticular RMS ipsilateral retroperitoneal lymph node dissection is mandatory. In children with IRS stage III and IV disease, feasibility of surgery is assessed after 4–5 cycles of neoadjuvant chemotherapy. Surgery is limited to situations where complete surgical resection of the postinduction chemotherapy mass may result in a meaningful reduction in the dose of postoperative radiation. In other instances, like large head and neck masses, local control is achieved by radiotherapy alone. For tumors arising in the bladder and prostate the goal is to preserve function without compromising local disease control.

RECURRENT RHABDOMYOSARCOMA

The majority of recurrences of RMS occur within the first 3 years of completing therapy. Although some children attain durable remissions with secondary therapy, the long-term prognosis for children with progressive or recurrent disease is extremely poor. The 3-year survival following relapse for patients is less than 15%. Various poor prognostic factors in recurrent RMS are early relapse, widespread disease at the time of relapse and intensity of initial treatment.

MANAGEMENT OF NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMA

Unlike RMS, which is a highly chemosensitive tumor, the mainstay of treatment of NRSTS is complete surgical resection with or without adjuvant radiotherapy. Wide local excision or en bloc resection with negative margins should be the aim in all children with NRSTS. Adequacy of margins is a debatable issue. In some areas such as head and neck, mediastinum and retroperitoneum, wide local excision with clear margins may be impossible to achieve without mutilating resections. The finding of microscopic involvement of surgical margins is highly predictive for local disease recurrence, distant disease recurrence and diminished overall survival. This is why primary re-excision is preferred over any adjuvant therapy. Unlike adults where radiotherapy is recommended for all cases of NRSTSs, radiotherapy in children is reserved for grade 3 or 4 tumors and those with compromised margins or recurrent disease. Role of chemotherapy in NRSTS is limited and is reserved for patient with systemic disease and specific histologic types like synovial sarcoma and malignant peripheral nerve sheath tumor. The most active agents in NRSTS include doxorubicin and ifosfamide.

Late Effects

With improvements in the outcome of patients with STS with multimodality approach and systematic multicentric clinical trials, there is growing concern regarding potential late effects associated with the treatment. Major issues that need to be considered during treatment include growth and development, infertility, second malignancy and functional integrity of vital organs. Monitoring for late effects is important in long-term survivors of STS.

PROGNOSTIC FACTORS AND OUTCOME

Rhabdomyosarcoma is curable in the majority of children receiving optimal therapy (70% survival 5 years after diagnosis). Extent of disease is the most important prognostic factor. Those with metastatic disease at diagnosis have the worst prognosis **(Table 6)**. The other unfavorable prognostic factors are alveolar histology, large primary tumor (> 5 cm), unfavorable location, age less than 1 year or more than 10 years and incomplete surgery (R1 resection). The event free survival by risk group ranges from more than 85% (low-risk) to less than 30% (high-risk) **(Table 6)**. Unfavorable prognostic factors for NRSTSs include metastatic disease, involvement of regional lymph node, tumor size > more than 5 cm, high grade histology and positive surgical margins.

Table 6 COG-STS rhabdomyosarcoma risk group classification

Risk group prognosis (Event-free survival)	Histology	Stage	Group
Low-risk Excellent (70–> 85%)	Embryonal Embryonal	1 2, 3	I, II, III I, II
Intermediate-risk Good (50–70%)	Embryonal Alveolar	2, 3 1, 2, 3	III I, II, III
High-risk Poor (< 30%)	Any	4	IV

IN A NUTSHELL

1. Soft tissue sarcomas (STS) in children are broadly classified as rhabdomyosarcoma (RMS) and nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) and constitute 7% of all pediatric cancers in the West (lower percentage in India).
2. High index of suspicion and early referral by the general physician/pediatrician are important steps in ensuring high cure rates.
3. Symptoms at presentation include painless progressive lump and or pressure symptoms depending on anatomic site of origin.
4. Initial work-up includes local imaging followed by biopsy for confirmation of diagnosis.
5. Proper staging and risk stratification are essential to formulate the treatment plan.
6. Treatment includes multidisciplinary approach with coordinated efforts from pediatric oncologist, surgeon, radiotherapist and pathologist.
7. Systemic chemotherapy is the backbone of treatment for RMS and local control is provided with radiotherapy and/or surgery.
8. Primary modality of treatment for NRSTS is surgery and other modalities (radiotherapy or chemotherapy) are reserved for selected patients.
9. Patients with nonmetastatic RMS have high cure rates with multimodality treatment, while most children with metastatic disease have dismal outcome.
10. Monitoring for late effects is important in long-term survivors of STS.

MORE ON THIS TOPIC

Dantonello TM, Int-Veen C, Winkler P, et al. Initial patient characteristics can predict pattern and risk of relapse in localized rhabdomyosarcoma. J Clin Oncol. 2008;26:406-13.

Davicioni E, Anderson MJ, Finckenstein FG, et al. Molecular classification of rhabdomyosarcoma–genotypic and phenotypic determinants of diagnosis. A report from the Children's Oncology Group. Am J Pathol. 2009;174:550-64.

Ferrari A, Casanova M. Current chemotherapeutic strategies for rhabdomyosarcoma. Expert Rev Anticancer Ther. 2005;5:283-94.

Puri DR, Wexler LH, Meyers PA, et al. The challenging role of radiation therapy for very young children with rhabdomyosarcoma. Int J Radiation Oncol Biol Phys. 2006;65:1177-84.

Raney RB, Anderson JR, Barr FG, et al. Rhabdomyosarcoma and undifferentiated sarcoma in first two decades of life: a selective review of intergroup rhabdomyosarcoma study group experience and rationale for Intergroup Rhabdomyosarcoma Study V. J Pediatr Hematol Oncol. 2001;23:215-20.

Spunt SL, Hill DA, Motosue AM, et al. Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. J Clin Oncol. 2002;20:3225-35.

Spunt SL, Skapek SX, Coffin CM. Pediatric nonrhabdomyosarcoma soft tissue sarcomas. Oncologist. 2008;13:668-78.

Wexler LH, Meyer WH, Helman LJ. Rhabdomyosarcoma and the undifferentiated sarcomas. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott-Raven; 1997. pp. 923-53.

Chapter 45.13
Histiocytic Disorders
Gaurav Narula, Nirmalya D Pradhan

Histiocytic disorders of childhood encompass a broad group of disorders having their common origin from activated cells of the monocyte macrophage system, resembling histiocytes. Early in development common myeloid progenitor cells of the monocyte macrophage system divide into two lines based on CD1a acquisition. The positive cells get committed to form Langerhans cells (LCs) from which Langerhans cell histiocytosis (LCH) originates. The CD1a negative cells acquire CD14 and then based on their location, develop into either dermal or interstitial dendrocytes, or macrophages in the hematological and lymphoreticular systems. The former is the cell of origin for juvenile xanthogranuloma (JXG) and Erdheim-Chester disease, while the latter is incriminated in hemophagocytic lymphohistiocytosis (HLH) and sinus histiocytosis with massive lymphadenopathy (SHML or Rosai-Dorfman disease). Of these only LCH, HLH and SHML will be discussed here as being more relevant to children.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis is an enigmatic disorder of uncertain origin and myriad presentations. Their characteristic feature is the presence of LCH cells in a background of hematopoietic cells, which include T-cells, macrophages and eosinophils, sometimes present in sheets, and occasional multinucleated giant cells, leading to the term eosinophilic granulomas in the past. The clonal proliferation of LCH cells may represent a true malignancy or immune dysregulation of LCs.

The disease was called by different names based on descriptions and descriptors (e.g., Letterer-Siwe disease, Hand-Schüller-Christian, eosinophilic granuloma, etc.). The term histiocytosis X was first suggested by Lichtenstein thereby acknowledging both facts in the name—*histiocytosis* emphasizing their common origin, and *X* underlining his uncertainty about what the origin was. A common etiology is now well identified and minimum diagnostic criteria have evolved. LCH is divided into risk groups by the organs involved at diagnosis with liver, spleen, lung, and bone marrow, traditionally being associated with poor outcomes. Recently lung has been dropped as a *risk-organ*.
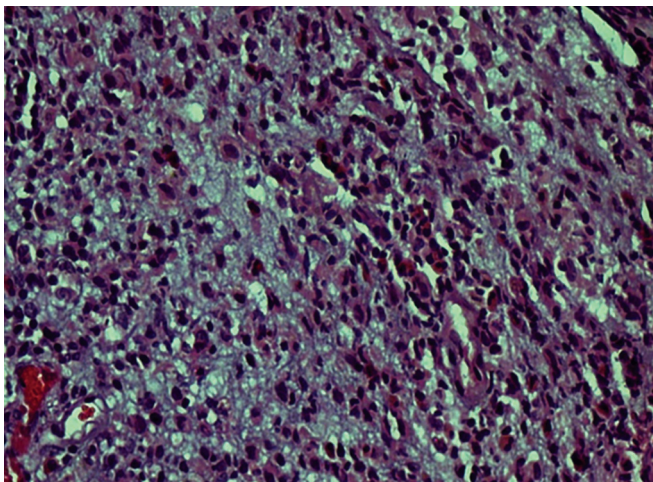
Epidemiology

The reported incidence of LCH from various studies is 2–10/million below 15 years of age, with a median presentation at 2½ years. The sex ratio is close to one. Data for incidence in India is lacking though most large cancer centers report seeing 5–10 patients per year. There is a weak association of LCH with parental solvent exposures, and perinatal infections. A family history of cancer may also contribute to a slightly higher incidence.

Etiopathogenesis

A weak genetic association in the etiology of LCH is suggested by evidence of family clustering and a slightly higher than expected incidence in monozygotic twins. A stronger association exists between the single system phenotype and human leukocyte antigen (HLA) DRB1*03. However, no known racial predilection for LCH exists. While some insist on a genetic basis resulting in defective immune function, others suggest, it is a primarily reactive disorder with aberrant reactions between LCs and T-cells in response to environmental or other triggers. These triggers may be in the form of infections in childhood, or smoking in adults, which has been associated with lung LCH.

Pathology

The diagnosis of LCH is made based on the presence of histiocytes, the *LCH cells*, usually surrounded by a reactive infiltrate. This reactive infiltrate consists of macrophages, lymphocytes, eosinophils, giant cells and, less commonly, neutrophils and plasma cells **(Fig. 1)**. The overall picture may, however, vary widely, making the diagnosis difficult on morphology alone.

The identifying feature of LCH cells are *Birbeck granules* which can be seen only on electron microscopy. They may not be present in all LCH lesions, varying widely from 2% to 69% and their absence cannot be construed as exclusion of LCH. Flow cytometric analysis and immunohistochemistry (IHC) can detect CD1a, which is considered pathognomonic **(Fig. 2)**. Positivity for S100 is also common, but is less specific. Eosinophils may be absent and are not essential for a diagnosis of LCH, paradoxical as this may sound for a so-called *eosinophilic granuloma*. Presence of plasma cells, B-lymphocytes and neutrophils reflect a reaction to local tissue damage in the LCH process.

Clinical Features

The clinical presentations of LCH are wide and varied ranging from low grade chronic and persistent to the rapidly progressive and

Figure 1 Morphology of Langerhans cell histiocytosis (LCH) showing sheets of eosinophils and reactive cells
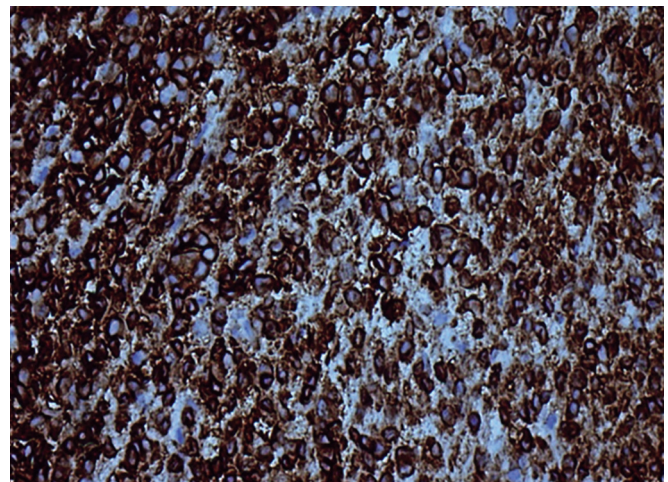
Figure 2 The same specimen as in Figure 1 showing strong reactivity for CD1a on immunohistochemistry

fatal course. Involvement of certain *risk*-organs like liver, spleen, and bone marrow gives it a more aggressive behavior, resulting in disease progression, sequelae and death. In contrast, organs like skin, skeletal system, lymphatic system, the gastrointestinal (GI) tract, pituitary gland, and central nervous system (CNS), are considered *low-risk*. The number of organs may be limited to one, and this may be at a single site (unifocal) or multiple sites (multifocal).

Single-system Disease

In single-system disease (SS-LCH), a single site or organ is involved, usually the skin, oral cavity, skeletal and lymphatic systems, or endocrine glands like the thyroid and pituitary glands. Skin is involved in 35–50% cases in most series. Seborrheic involvement of the scalp is often mimicked by cradle cap in infants. Sometimes papular lesions, brown to purplish in appearance may appear over any part of the body and they may remit spontaneously by 1–2 years of age (Hashimoto-Pritzker disease). Older children may present with a papular rash in the groin, abdomen, back, or chest. Seborrheic involvement of the scalp is often mistaken as dandruff. Ulcerative lesions in crevices and creases such as the groin and perianal region, behind the ears and under the breasts mimic bacterial or fungal infections.

Oral cavity lesions may be a presenting feature. The gingiva is hypertrophied and ulcerations may develop in any part of the oral cavity. Maxillary and mandibular lesions may loosen the teeth making them hypermobile (floating teeth) and cause premature tooth loss.

The skeletal system is the most common site of involvement in LCH, seen in 80–100% of patients. Flat bones like skull and axial skeleton are preferentially involved over long bones, while hands and feet are almost never affected **(Fig. 3)**. The usual presentation is a lytic bony lesion with associated soft tissue swelling, which may be asymptomatic or painful. Lesions in the vertebra often have soft tissue extensions and may cause compressive neuropathies. Facial bones and the base of skull lesions with intracranial tumor extension lend a higher risk of developing diabetes insipidus and neurodegenerative syndrome and are grouped as *CNS-risk* lesions.

Lymphadenopathy is more common in Indian series than in western literature, where it is less than 10%. Cervical nodes are the most frequent. Nodes may mimic several conditions appearing soft or hard on palpation, or even matted. Lymphedema may also be present. Enlarged nodes in the mediastinum and in infants

Figure 3 Lytic lesions in the skull

the thymus, can mimic infections or lymphomas. The posterior pituitary is rarely involved in isolation and presents with central diabetes insipidus, though it is more likely to occur as a part of multisystem LCH. Anterior pituitary involvement can present as growth failure.

Multisystem Disease

Involvement of more than one organ system constitutes multisystem disease. Involvement of the liver, spleen and hematological system (bone marrow) put the patients into a higher risk category. Other systems may be involved as in SS-LCH in any combination.

Gastrointestinal system Splenic involvement has been seen with higher frequency in India than in the European series. The spleen can sometimes become grossly enlarged resulting in hypersplenism with one or more cytopenias, and occasional respiratory compromise due to its size. Hepatomegaly is often present in multisystem disease. LCH in liver preferentially involves the bile duct causing damage to the biliary tract and can cause biliary damage leading to cholestasis and sclerosing cholangitis, which can be fatal. In the long-term there may be biliary sclerosis and cirrhosis. Rarely LCH may infiltrate the pancreas and kidneys. Other GI manifestations in LCH are diarrhea and malabsorption.

Lung Lung involvement is less common in children. In adults, smoking may play an etiologic role. Cytokine induced destruction of lung tissue causes cystic/nodular pattern of disease, which is usually symmetrical. The upper and middle lung fields are preferentially involved, while the costophrenic angles are spared. The cysts can form bullae which may rupture and cause spontaneous pneumothorax as a presenting feature. Other manifestations are progressive fibrosis leading to respiratory and ultimately ventilatory failure. Monitoring the diffusion capacity can detect early involvement and progress. The march of events can be stopped to some degree by treatment, and even allow some recovery of function.

Bone marrow Bone marrow involvement is more common in younger children with diffuse disease involving other risk-organs, the lymphatic system and skin. Thrombocytopenia and anemia in varying degrees may be seen. Isolated neutropenia is less frequent. Hemophagocytosis can often be seen in the bone marrow when involved with LCH.

Endocrine system The most frequent endocrine manifestation in LCH is diabetes insipidus, which occurs due to damage to the posterior pituitary antidiuretic hormone (ADH) secreting cells. Involvement is usually picked up by magnetic resonance imaging (MRI) and biopsies are not needed. LCH patients with diabetes insipidus have a 50–80% chance of developing other organ involvement diagnostic of the disease within 1 year of its onset.

Central nervous system Patterns of involvement in the CNS include mass lesions in the hypothalamic-pituitary region, choroid plexus, gray matter, or white matter. A small percentage of LCH patients ranging from 1% to 4% may develop a chronic neurodegenerative syndrome manifesting as dysarthria, ataxia, dysmetria, and sometimes behavioral changes. MRI findings such as hyperintensity of the dentate nucleus and cerebellar white matter on T2-weighted images or hyperintense lesions of the basal ganglia on T1-weighted images are characteristic.

Diagnostic Evaluation

A complete history and physical examination is essential and all systems must be thoroughly checked including the skin, which is often missed or misdiagnosed. Growth velocity should be checked and a history of polyuria and polydipsia must be explored.

The usual sites of biopsy are the lytic skeletal lesions, prominent skin lesions and lymph nodes. Occasionally, a liver biopsy may be indicated when there is liver dysfunction and hypoalbuminemia not otherwise explained, and a diagnosis of LCH cannot be established by other means. Lung biopsies are rarely needed. Apart from morphological evidence of involvement on biopsies from suspected lesions, special stains like anti-CD1a and/or anti-CD207 (langerin) and anti-CD163 immunostains must be used for confirmation of LCH cells. A complete skeletal survey should be done in all patients of LCH. Newer diagnostic imaging modalities like 18-fluorodeoxyglucose positron emission tomography (18F-FDG PET) scan can reliably pick-up diseases in all sites of involvement but have not replaced screening in standard practice yet **(Fig. 4)**. Computed tomography (CT) scan and MRI scans are done when indicated. A summary of minimal diagnostic evaluation for a case of LCH is given in **Table 1** and definitions of risk-organ involvement in **Table 2**.

Treatment

Treatment of LCH is determined by the organ systems and the combinations in which they are involved. Historically, all modalities of treatment in oncology including surgery, radiation and chemotherapy have been used. Consensus now has brought down the options to chemotherapy alone, with the surgical option of curettage employed for the rare solitary bone lesion, or a solitary lymph node where the biopsy itself proves therapeutic. When only low-risk organs are involved like skin, lymph nodes and bones in isolation, therapy is usually given for 6 months. When risk-organs such as spleen, liver and bone marrow are involved, then treatment duration is increased with a maintenance phase to 1 year or beyond. Another crucial thing in their management is to have an early response to therapy assessment, usually at 6 weeks, in which
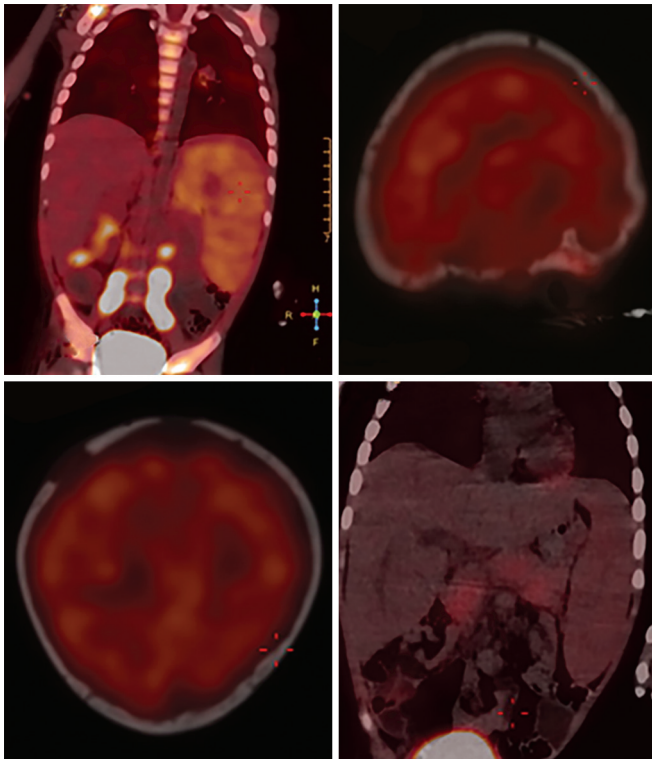
Figure 4 Positron emission tomography-computed tomography (PET-CT) scan showing disease activity in multiple sites including left scapula, bilateral ischium, abdominal lymph nodes and spleen, with lytic lesions in the skull vault in a case of multisystem high-risk Langerhans cell histiocytosis (LCH)

Table 1 Diagnostic evaluations in Langerhans cell histiocytosis (LCH)

History of polyuria or polydipsia	Early morning urine specific gravity and osmolality Blood electrolytes Water deprivation test if possible MRI of the head
Cytopenias	Bone marrow aspirate and trephine biopsy to exclude causes other than LCH Evaluation for macrophage activation and hemophagocytic syndrome
Liver dysfunction	MRI liver Liver biopsy
Lung involvement	High resolution-computed tomography (HR-CT) of lung Lung function tests (if age appropriate) Bronchoalveolar lavage (BAL): > 5% CD1a+ cells in BAL fluid may be diagnostic in a nonsmoker Lung biopsy (if BAL is not diagnostic)
Suspected craniofacial bone lesions including maxilla and mandible	MRI of head including the brain, hypothalamus–pituitary axis, and craniofacial bones CT scan involved bone and skull base (if MRI not available)
Aural discharge or suspected hearing impairment/mastoid involvement	Formal hearing assessment MRI of head or HR-CT of temporal bone
Vertebral lesions (even if only suspected)	MRI of spine to assess for soft tissue masses and to exclude spinal cord compression
Visual or neurological abnormalities	MRI head Neurological assessment Neuropsychometric assessment
Suspected endocrine abnormality (i.e., short stature, growth failure, hypothalamic syndromes, precocious, or delayed puberty)	MRI head Endocrine evaluation
Unexplained chronic diarrhea, failure to thrive, or malabsorption	Endoscopy Biopsy

(Adapted from Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013;60:175-84.

Table 2 Diagnostic criteria for risk-organ involvement in Langerhans cell histiocytosis (LCH)

Hematopoietic involvement (with/without bone marrow involvement)	At least two of the following: 1. Anemia Hb < 10 g/dL—children; Hb < 9 g/dL—infants (not due to other causes, e.g., iron deficiency) 2. Leukocytopenia $< 4 \times 10^9$/L 3. Thrombocytopenia $< 100 \times 10^9$/L
Spleen involvement	Enlargement > 2 cm below costal margin in midclavicular line
Liver involvement	Enlargement > 3 cm below costal margin in midclavicular line and/or
	Liver dysfunction (hypoproteinemia < 55 g/L, hypoalbuminemia < 25 g/L) not due to other causes) and/or Histopathological diagnosis
Lung involvement	Typical changes in HR-CT and/or Histopathological/cytological diagnosis

Note: Lung involvement is no longer considered a risk organ.
Abbreviation: HR-CT, high resolution-computed tomography.

there should be definite improvement or even complete response. Those with an intermediate response will require a second intensive phase, while those who progress must be taken up for salvage options including stem cell transplant at the earliest, as it is this group that remains at the highest risk for fatal outcome. Most of the data on treatment has come from the earlier German-Austrian-Dutch (Deutsche Arbeits-gemeinschaft für Leukaemieforschung und-therapie im Kindesalter [DAL]) Group trials, and later from the collaborative LCH trials of the Histiocyte Society. Even before the LCH trials, the DAL trials had already demonstrated the utility of maintenance of 1 year in which their patients had fewer relapses (29%), compared to the LCH-I and LCH-II trials, where relapse rates remained as high as 50% with a total treatment duration of 6 months. Indications of systemic therapy are shown in **Box 1**.

BOX 1 Indications for systemic therapy in Langerhans cell histiocytosis (LCH)

- SS-LCH with CNS-*risk lesions*
- SS-LCH with multifocal bone lesions (MFB)
- SS-LCH with special *site* lesions
- MS-LCH with/without involvement of *risk-organs*

Abbreviations: SS-LCH, single system-Langerhans cell histiocytosis; MS-LCH, multisystem-Langerhans cell histiocytosis.

Low-risk Langerhans Cell Histiocytosis (Single-system or Multisystem)

Patients with skin involvement only may be observed as the lesions resolve spontaneously. Various modalities of treatments for nonresolving skin lesions include topical steroids, oral methotrexate, oral thalidomide, topical application of nitrogen mustard, and psoralen with UV light.

High-risk Multisystem Disease

The length of therapy recommended for high-risk MS has evolved from the LCH-I, LCH-II, and the DAL-HX-83 studies before, and varies from 6 months (LCH-I and LCH-II) to 1 year (DAL-HX-83). Though the value of prolonged maintenance was established in the DAL-HX studies, it was not incorporated into standard practice as it was not a randomized controlled trial, and it was not until the high relapse rates of the LCH I and II trials were noticed that a prolonged maintenance was used in a randomized fashion in LCH III. The LCH-II study also looked in a randomized way at a standard induction of vinblastine and prednisolone in one arm versus additional mercaptopurine or etoposide for high-risk patients. As no additional benefit was found in outcomes (response at 6 weeks, 5-year probability of survival, relapses, and permanent consequences) between the two treatment groups, etoposide was dropped from further LCH studies, especially given its second malignancy risk. The LCH-III study randomized risk-organ affected patients to vinblastine/prednisone/6-mercaptopurine or vinblastine/prednisone/6-mercaptopurine plus methotrexate (intravenous during the induction phase and oral in the continuation phase). The response rates at 6 and 12 weeks and overall survival were not improved.

Treatment of CNS Disease

To successfully treat CNS-LCH, drugs which can effectively cross the blood brain barrier are required. These include cladribine (2-CdA), or other nucleoside analogs, such as cytarabine. However, before beginning treatment, it must first be observed that the lesions are symptomatic and showing signs of progression, as there is little evidence that early treatment of asymptomatic CNS disease affects its course.

Treatment Response Assessment

Response to treatment assessment is still difficult in LCH therapy unless specifically evaluated clinically or radiologically. Skeletal lesions are slow to heal, and plain radiographs can be misleading. They sometimes show sclerosis at the periphery of the bony lesion, which can be taken as a sign of healing. Soft tissue lesions and pulmonary involvement are better followed up on CT scans. MRI is the best modality to follow-up response in the same indications it was needed upfront. In addition, pulmonary function testing and monitoring for diabetes insipidus must be undertaken at all re-evaluation points. Based on the disease activity on re-assessment, the disease state and response is categorized **(Table 3)**. Scheme for treatment of multisystem LCH based on response assessment is given in **Flow chart 1**.

Treatment of Recurrent, Refractory, or Progressive LCH

Treatment in recurrent, refractory or progressive LCH is more difficult and the best options are still to be determined. The various setting in which this may occur are given as follows:

Recurrent low-risk-organ involvement Such patients can be given a reinduction of vinblastine and prednisone for 6 weeks, and if they have a good response then a longer maintenance of at least 1 year should be given with 3-weekly vinblastine and a short pulse of steroids and daily oral mercaptopurine. In recurrent multifocal bone disease and low-risk MS-LCH, cladribine (2-CdA) has also been effectively used with sustained remission. Other drugs used in maintenance are indomethacin and bisphosphonates.

Refractory high-risk-organ involvement MS-LCH patients with risk-organs involved having progression or only intermediate response at 6 weeks require an early change of plan, as they have only 10–50% chance of survival. Intensive acute myeloid leukemia (AML) type protocols have been used with some success in these patients, of which 2-CdA and/or Ara-C are most likely to impact overall survival. In patients showing progression or intermediate response at 6 weeks after salvage therapy, hematopoietic stem cell transplantation, usually reduced intensity, must be considered if a sibling is available and funding can be arranged.

Late Disease and Treatment Effects of Childhood LCH

Chances of developing long-term sequelae in children with low-risk and high-risk organ involvement are approximately 20% and 70% respectively. Long-term neurologic sequelae are hypothalamic/pituitary dysfunction, cognitive dysfunction, cerebellar involvement, hearing loss, behavior abnormalities and deficit in short-term memory. Patients with diabetes insipidus are at increased risk for developing panhypopituitarism. These patients need careful monitoring for adequacy of growth and development. Growth and development problems are more when the disease presents in infants and adverse effects of long-term steroids may also play a role.

Table 3 Definition of disease state and response of Langerhans cell histiocytosis (LCH)

No active disease (NAD)	No evidence of disease	Resolution of all signs and symptoms
	Regressive disease	Regression of signs, symptoms, no new lesions
Active disease (AD)	Stable disease	Persistence of signs, symptoms, no new lesions
	Progressive disease	Progression of signs, symptoms and/or appearance of new lesions

Flow chart 1 Scheme for management of multisystem Langerhans cell histiocytosis (MS-LCH)
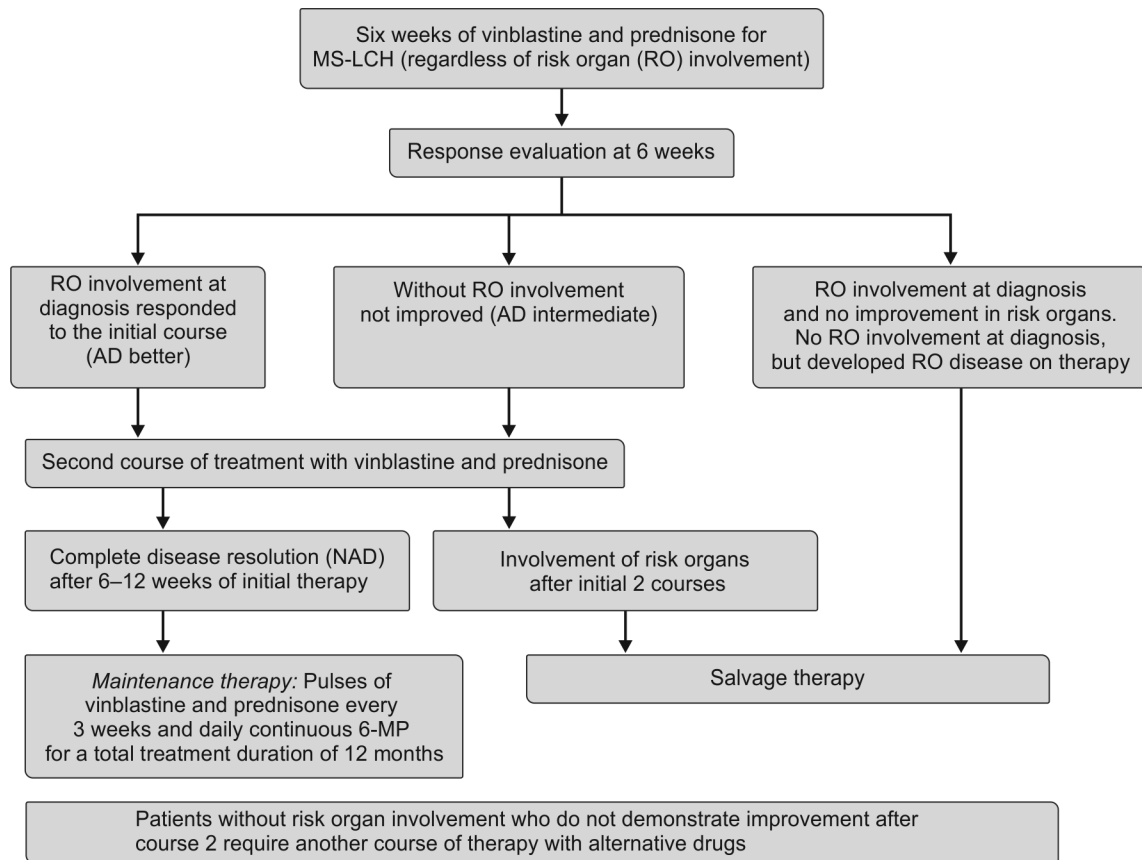
Abbreviations: AD, active disease; NAD, no active disease.

Bone lesions can often lead to permanent sequelae including vertebral collapse and spinal instability and deformation, or facial or limb asymmetry, which may be seen in 20% of patients. Diffuse pulmonary LCH can have permanent consequences due to poor pulmonary function, decreasing exercise tolerance and making them more prone to respiratory infections. Sclerosing cholangitis due to hepatic involvement by LCH can progress even after the disease has become quiescent and may require liver transplantation. Bone marrow failure may sometimes occur either due to disease or therapy. It is, however, a rare complication and often heralds a second malignancy. Second malignancies occur at a higher than normal frequency and include leukemia (more often AML) and lymphoblastic lymphoma. Solid tumors like retinoblastoma, brain tumors, hepatocellular carcinoma, and Ewing sarcoma may occur.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis is an uncommon life-threatening hematological disorder. It is an inflammatory disorder caused by uncontrolled proliferation of activated lymphocytes and macrophages secreting various inflammatory cytokines. HLH may be primary (familial HLH) or secondary (acquired HLH).

Primary HLH is an autosomal recessive disorder more prevalent with parental consanguinity. Five genetic subtypes of FHLH have been described the most well-documented one being FHLH type 2-associated PRF1 (perforin) gene mutation. 70% of FHLH manifest during infancy. Family history of sibling death

due to unknown cause may be present. Bone marrow transplant is the only treatment option for FHLH.

Secondary HLH may be due to infections (malaria, leishmania, bacterial, fungal) or malignancies (lymphoma, leukemia). Specific cause directed therapy may cause disease remission in secondary HLH. The aim of treatment is to suppress the severe inflammation caused by various stimuli. Apart from leishmaniasis, patients also require HLH directed therapy. Most of the current regimens use corticosteroids, etoposide, cyclosporine and intrathecal therapy and intravenous immunoglobulin (IVIG). Bone marrow transplantation is required for relapsing secondary HLH.

Patients with HLH present with fever, hepatosplenomegaly and lymphadenopathy, associated with cytopenias, liver dysfunction, coagulopathies and metabolic disturbances often overlapping the underlying disorder making diagnosis difficult. The diagnostic features are summarized in **Table 4**. Prognosis of HLH is very dismal with an overall mortality of about 50%. Treatment is with aggressive supportive care for coagulation defects, anemia and thrombocytopenia with blood and blood products, fluid and electrolytes management, along with specific therapy. The latter includes chemotherapy and immunotherapy with drugs like etoposide along with steroids, IVIG and cyclosporine. The triggering cause such as leukemia or infection, would need to be treated simultaneously, making the entire management very complex and can usually be carried out only in centers with the requisite expertise. Stem cell transplant is the only recourse for those refractory to treatment or relapsing early.

Table 4 Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH)

1. Molecular diagnosis consistent with HLH, i.e., presence of mutation of *PRF1*, *UNC13D* or *STX11*
Or

2. Presence of 5 out of 8 criteria
    a. Fever
    b. Splenomegaly
    c. Cytopenias
    d. Hypertriglyceridemia (fasting triglyceride ≥ 265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤ 1.5 g/L)
    e. Raised ferritin level (≥ 500 µg/L)
    f. Hemophagocytes in bone marrow, spleen or lymph node
    g. Low or absent NK-cell activity
    h. Increased level of CD25 also known as IL-2 receptor (≥ 2400 U/mL)

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY OR ROSAI-DORFMAN DISEASE

Sinus histiocytosis with massive lymphadenopathy is a rare disorder of unknown etiology. It is characterized by presence of abundant histiocytes in lymph nodes. Patients present with lymphadenopathy with cervical lymph nodes being the most common site. Uncommon extranodal sites of disease are skin, upper respiratory tract, spleen, testes, CNS, parotid gland, bone and sinuses **(Fig. 5)**. Immunological abnormalities with autoimmune disorders like autoimmune cytopenias, glomerulonephritis, amyloidosis or arthritis may present in few patients.

Lymph nodes in SHML shows marked dilatation of sinuses with sinus histiocytes with prominent phagocytosis of intact lymphocytes, plasma cells and erythrocytes called emperipolesis which is usually pathognomonic of SHML. About 20% patients show spontaneous resolution within few months. Majority of patients have stable persistent disease and do not warrant any therapy. Patients having autoimmune manifestations and extranodal involvement at presentation have a fatal outcome. Various treatment options for progressive disease or symptomatic patients are corticosteroids, 6-mercaptopurine, methotrexate, cladribine and alpha interferon.

Figure 5 A case of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Note the lesion below the left orbit also

IN A NUTSHELL

1. Histiocytic disorders of childhood are a complex group of rare disorders linked to the cell of origin from the macrophage and histiocyte lineage.
2. The most common ones affecting children are Langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH) and sinus histiocytosis with massive lymphadenopathy (SHML).
3. LCH is rare and has myriad presentations, which can broadly be divided into single system (SS-LCH), and multisystem (MS-LCH). The latter may occur with or without risk-organ involvement. *Risk organs* are liver, spleen and bone marrow.
4. Multifocal bone (MFB) disease and CNS risk LCH form two special groups, which tend to behave differently from other organ involvement.
5. Chemotherapy is required for MS-LCH, MFB and CNS risk disease when progressive, requires treatment with chemotherapy and steroids.
6. MS-LCH with risk organ involvement can have an aggressive course and early response assessment with prompt second-line and salvage options in refractory cases is the only chance for cure in this subgroup. Even then, mortality remains high.
7. Sequelae can be expected in MS-LCH with risk organs and CNS risk disease. Common problems are bone deformations, endocrine disorders including diabetes insipidus (DI) and growth failures, chronic respiratory disorders and liver failure.
8. HLH is an aggressive disease, which may be familial or acquired. FHLH presents early, with strong family history and is fatal unless treated promptly and followed by stem cell transplantation.
9. Secondary HLH also is an aggressive disease, requiring simultaneous management of several factors including the primary cause, which is best done in specialized centers.
10. SHML is a benign disease that can occasionally result in significant cosmetic deformity or compromise of vessel or airway depending on location, warranting treatment, which is primarily aimed at cytoreduction.

MORE ON THIS TOPIC

A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child.1996;75:17-24.

Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin N Am.1998;12:247-58.

Gadner H, Grois N, Pötschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood. 2008;111:2556-62.

Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013;121:5006-14.

Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013;60:175-84.

Laman JD, Leenen PJ, Annels NE, et al. Langerhans-cell histiocytosis' insight into DC biology. Trends Immunol. 2003;24:190-6.

Lichtenstein L. Histiocytosis X: integration of eosinophilic granuloma of bone, Letterer–Siwe disease and Schuller–Christian disease as related manifestations of a single nosologic entity. Am Med Assoc Arch Pathol.1953;56:84-102.

Minkov M, Grois N, Heitger A, et al. Treatment of multisystem Langerhans cell histiocytosis. Results of the DAL-HX 83 and DAL-HX 90 studies. DAL-HX Study Group. Klin Padiatr. 2000;212:139-44.

Narula G, Bhagwat R, Arora B, et al. Clinico-biologic profile of Langerhans cell histiocytosis: a single institutional study. Indian J Cancer. 2007;44:93-8.

Willis B, Ablin A, Weinberg V, et al. Disease course and late sequelae of Langerhans' cell histiocytosis: 25-year experience at the University of California, San Francisco. J Clin Oncol.1996;14:2073-82.

Chapter 45.14
Bone Tumors
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Primary malignant bone tumors are extremely rare, accounting for only 0.2% of tumors across all age groups. These tumors mainly affect children and adolescents and the etiology of these tumors is essentially unknown. The diagnosis and treatment of bone tumors; whether benign or malignant, is complex and requires a seamless multidisciplinary approach between various fields including orthopedic surgery, radiology, pathology, pediatric (or medical) oncology, radiation oncology and rehabilitation services. Due to the complexities related to the diagnosis and management, these tumors are best managed at specialist tumor treating centers. An integrated multispecialty approach to the diagnosis and treatment of these intriguing lesions helps to formulate a rational and logical management plan to offer the best oncological and functional outcome. This strategy has resulted in a tremendous improvement in survival of these patients over the last few decades. In addition, advent of effective multiagent chemotherapeutic protocols; advances in radiotherapy, improvement in radiology and pathology techniques have all contributed to the improved outcomes. Technological advances to provide durable megaprosthesis has made limb salvage a norm in today's era.

EPIDEMIOLOGY

Bone sarcomas are rare and account for only 0.2% of all neoplasms (all ages) as per the SEER database and the annual incidence rate is approximately 0.8 new cases per 100,000 population. In pediatric oncology, bone tumors account for 6–8% of all malignancies seen in less than 15 years of age. In children and adolescents osteosarcoma is the most common primary malignant tumor of bone, followed by Ewing sarcoma. Chondrosarcoma is a disease of the mature skeleton and hence is uncommon in children and adolescents.

Malignant bone tumors vary in the incidence by age. Osteosarcomas show a bimodal peak in the rate of occurrence, first being the well-defined peak occurring in second decade of life, and the second peak in older patients in fifth and sixth decade. While appendicular skeleton is the most common site of affection accounting for 80% of cases during the first peak, it is a less common site (less than 50%) during the second peak (older patients). Unlike osteosarcoma, Ewing sarcoma has a unimodal distribution of occurrence with children and adolescents in first and second decades affected the most. This incidence dramatically decreases after skeleton maturity. Osteosarcoma mainly affects the metaphysical region of bone while Ewing sarcoma usually involves diaphysis. There is no published data on the exact incidence of bone tumors in children from India.

ETIOPATHOGENESIS

The exact etiology of bone tumors is still unknown. Although various theories have been proposed to establish the etiopathogenesis, most of the bone tumors are considered sporadic in origin. Factors predisposing to the occurrence of these bone tumors are listed in **Table 1**. Like neoplasms occurring in other areas, bone tumors too may be benign or malignant. Benign tumors are generally slow growing and rarely metastasize. Malignant bone tumors are biologically more aggressive, cause rapid local destruction and have high tendency of spread and metastasis. Bone tumors can be classified based on their cell of origin. The main cells of origin include, cartilage cells, osteoblastic cells, fibroblastic cells, primitive mesenchymal cells, and hematopoietic cells, as well as

Table 1 Factors predisposing to occurrence of bone tumors in children and adults

- Ollier disease (enchondromatosis) and Maffucci syndrome
- Familial retinoblastoma syndrome
- Li-Fraumeni syndrome
- Rothmund-Thomson syndrome
- Multiple osteochondromas
- Paget disease
- Radiation
- Bone infarction
- Chronic osteomyelitis
- Osteogenesis imperfecta

nerve and vascular tissue, notochordal remnants, and other rare sites. The classification of bone tumors across all age groups based on the cell of origin is tabulated in **Table 2**.

CLINICAL FEATURES

Children with bone tumors mainly present with either one or all of the following clinical features—pain; palpable mass (swelling); loss of function (weight bearing and movement); pathological fracture; symptoms suggestive of disseminated disease; or incidental detection. A patient with a bone tumor initially complains of pain, swelling (palpable mass) and/or an alteration in his functional capability of weight bearing or movement. Benign tumors generally present with a palpable mass that may or may not be associated with pain. These tumors will have an indolent course and some of them may be diagnosed incidentally on radiographs. Malignant tumors usually have symptoms of pain first which is followed by rapidly progressive swelling. Many a time children and adolescents with early symptoms are diagnosed to have a sports injury or labeled as *growing pains*. The pain typically is worse at night and is progressive. Due to large swelling in juxta-articular area there may be associated restriction of joint movement. Pathological fracture occurring due to trivial trauma in a diseased bone leads to loss of ability to walk and may be the presenting symptoms in about 10% of cases. Large tumors may have associated skin changes like dilated superficial veins and stretch marks.

Tumors of the axial skeleton may have varied clinical presentations based on the site of occurrence. These include bowel and bladder disturbances (pelvic tumors), symptoms of spinal cord compression (spinal tumors), breathlessness or chest pain (chest wall tumors), and cranial nerve palsies or raised intracranial pressure (skull base and calvarial lesions). Patient with disseminated disease may present with multiple bone pains, weight loss, pyrexia and symptoms secondary to pancytopenia (bone marrow infiltration).

DIFFERENTIAL DIAGNOSIS

These include: infection—tuberculosis, osteomyelitis; trauma; bone cyst: simple bone cyst, aneurysmal bone cyst; metabolic bone disease; fibrous dysplasia; eosinophilic granuloma (Langerhans cell histiocytosis); other benign bone tumors.

EVALUATION AND DIAGNOSIS

The evaluation and diagnosis of bone tumors is rather complex and needs a multipronged strategy involving clinical, radiological and pathological approach. A detailed clinical history stating the mode of onset and progression of the disease may clinch the diagnoses

Table 2 Classification system for common bone tumors (all ages) based on the tissue of origin

Tissue of origin	Benign	Intermediate	Malignant
Osteoid (Osteogenic tumors)	Osteoma, osteoid osteoma	Osteoblastoma (locally aggressive)	Osteosarcoma
Cartilage (Chondrogenic tumors)	Osteochondroma, chondroma, enchondroma, periosteal chondroma, osteochondromyxoma, subungual exostosis, bizarre parosteal osteochondromatous proliferation, synovial chondromatosis	Locally aggressive: Chondromyxoid fibroma, atypical cartilaginous tumor/chondrosarcoma grade I rarely metastasizing: Chondroblastoma	Chondrosarcoma grade II, grade III, dedifferentiated chondrosarcoma, mesenchymal chondrosarcoma, clear cell chondrosarcoma
Fibroblastic (Fibrogenic tumors)	Fibroma	Desmoplastic fibroma (locally aggressive)	Fibrosarcoma
Vascular (Angiogenic tumors)	Hemangioma	Epitheloid hemangioma (locally aggressive, rarely metastasizing)	Epitheloid hemangioendothelioma, Angiosarcoma
Osteoclastic (Giant cell rich tumors)	Giant cell lesion of the small bones	Giant cell tumor of bone (locally aggressive, rarely metastasizing)	Malignancy in giant cell tumor of bone
Hematopoietic neoplasms			Plasma cell myeloma, solitary plasmacytoma of bone, primary non-Hodgkin lymphoma
Notochord	Benign notochordal tumor		Chordoma
Unknown (Tumors of undefined neoplastic nature)	Simple bone cyst, fibrous dysplasia, osteofibrous dysplasia, chondromesenchymal hamartoma, Rosai-Dorfman disease	Aneurysmal bone cyst, Langerhans cell histiocytosis, monostotic, polyostotic, Erdheim-Chester disease	Ewing sarcoma, adamantinoma, undifferentiated high-grade pleomorphic sarcoma of bone

in large number of cases. This clinical information should act as a compliment to radiological investigations, to reach a logical clinicoradiological diagnosis.

The goals of clinical evaluation and diagnostic work-up are:
- To reach a correct diagnosis
- To stage the local disease by assessing its extent
- To assess the distant spread of the disease
- To formulate a treatment plan
- To know the prognosis of the disease
- To counsel the patient and family regarding the treatment, related complication and probable prognosis.

Plain radiograph in two perpendicular planes spanning the entire length of bone and adjacent joint is the first ideal investigation for arriving at a diagnosis in bone tumors. A classical high grade osteosarcoma will appear as an osteoblastic or a mixed osteoblastic and osteolytic eccentrically placed lesion in the metaphyseal region of a long bone. This is due to destruction of normal bone architecture and production of abnormal osteoid. Infrequently these tumors may develop in the diaphyseal region. An osteosarcoma lesion usually demonstrates features of an aggressive lesion like cortical breach, permeative growth pattern, indistinct margins, extraosseous soft tissue extent and typical periosteal reaction in form of *sunburst* appearance and Codman's triangle **(Fig. 1)**. There may be associated pathological fracture and deformity of the bone. Ewing sarcoma generally appears as aggressive, nonmatrix producing lesion located usually in the diaphysis of the bone. These tumors demonstrate permeative destruction and an aggressive periosteal reaction that is described as *onion-peel* **(Fig. 2)**. These classical radiographic features may not be apparent in disease located in the axial skeleton.

Magnetic resonance imaging (MRI) is the most useful investigation for further characterization of the lesion due to its excellent soft tissue contrast, its sensitivity to bone marrow and soft tissue edema, and its multiple imaging planes. It also helps to determine the tumor relation with the adjacent neurovascular structures and to detect skip lesions and is useful in helping

the surgeon decide on the extent of the intramedullary as well as extramedullary disease which is eventually very essential for surgical planning **(Fig. 3)**. Benign tumors do not require metastatic work-up due to their inherent indolent nature and inability to metastasize. Malignant bone tumors are staged with computed tomography (CT) scan of the chest and a Tc-99m bone scan to rule out pulmonary and skeletal metastasis respectively. Newer modalities like positron emission tomography (PET) and whole body MRI scan are being evaluated for early identification of metastatic or multifocal disease. Bone marrow examination to look for infiltration by the tumor is also recommended in staging of Ewing sarcoma and is unwarranted in osteosarcoma. About 25% of

Figure 1 Osteosarcoma of distal femur. Radiograph shows characteristic radiological features of osteosarcoma including metaphyseal site of involvement, aggressive periosteal reaction (Codman triangle and sunburst appearance), osseous and extra- osseous soft tissue ossification

bone sarcomas are metastatic at presentation and the prognosis of these cases is significantly inferior to nonmetastatic ones.

Histopathological confirmation of a clinicoradiological diagnosis is the final step in the evaluation of a bone tumor case. It is ideal to complete all the diagnostic and staging imaging procedures before the biopsy in order to provide all the relevant information to the pathologist. In addition, an early biopsy may cause local hematoma and tissue edema, which may significantly alter the radiological image. A biopsy should be done to obtain adequate material in the least traumatic way. A core needle biopsy with *Jamshidi* (J) needle is preferred. The procedure can be done under

local anesthesia with minimal risk of soft tissue contamination and infection. Ideally, all the biopsies of suspected malignant tumors should be done by or under the supervision of the surgeon who is trained in performing limb salvage procedures and in centers where the definitive surgical management is going to be undertaken.

Histopathologically, osteosarcoma is composed of spindle, round, epithelioid, polygonal, multinucleate cells. These tumor cells are hyperchromatic and show nuclear atypia. The hallmark of osteosarcoma is the presence of malignant osteoid which is dense, pink and amorphous material. This is often *filigree-like* and juxtaposed to the atypical tumor cells. Ewing sarcoma is composed of sheets of small round blue cells with pale and indistinct cytoplasmic borders and small hyperchromatic nuclei and may also show rosette formation occasionally. Periodic acid-Schiff staining is often positive due to the presence of intracellular glycogen. The tumor cells on immunohistochemistry express CD 99 (MIC2) and FLI1 and also can rarely show focal cytokeratin positivity.

About 90% of Ewing sarcoma show a characteristic translocation t(11;22) (q24;q12). The translocation leads to fusion of the *EWS* gene with the transcription factor gene *FLI1*. The fusion transcript EWS-FLI1 can be detected in biopsy specimens by polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH). This technique has now become very helpful in differentiating Ewing sarcoma from other small round blue cell lesions such as lymphoma, neuroblastoma, rhabdomyosarcoma and poorly differentiated synovial sarcoma.

Staging Systems

The staging system used for malignant bone tumors proposed by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer is illustrated in **Tables 3 and 4**.

Figure 2 Ewing's sarcoma distal end of tibia. Radiograph shows laminated periosteal (*onion-peel*) reaction, permeating destruction with wide zone of transition
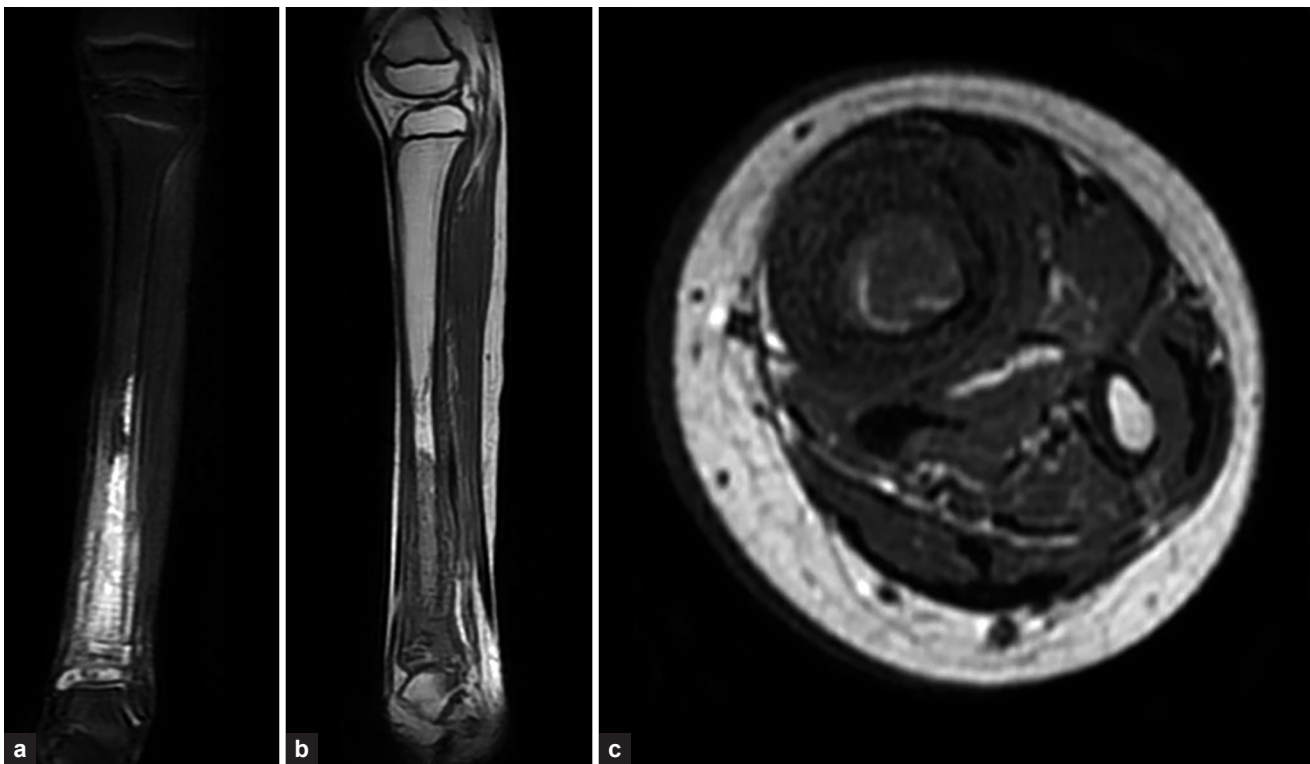
Figure 3A (a to c) Ewing's sarcoma distal end of tibia. Magnetic resonance imaging: (a) Coronal T2-weighted image; and (b) Sagittal T1-weighted image showing the intramedullary extent of disease; (c) T1-weighted axial image showing osseous involvement with minimal circumferential soft tissue component. Neurovascular bundle is free
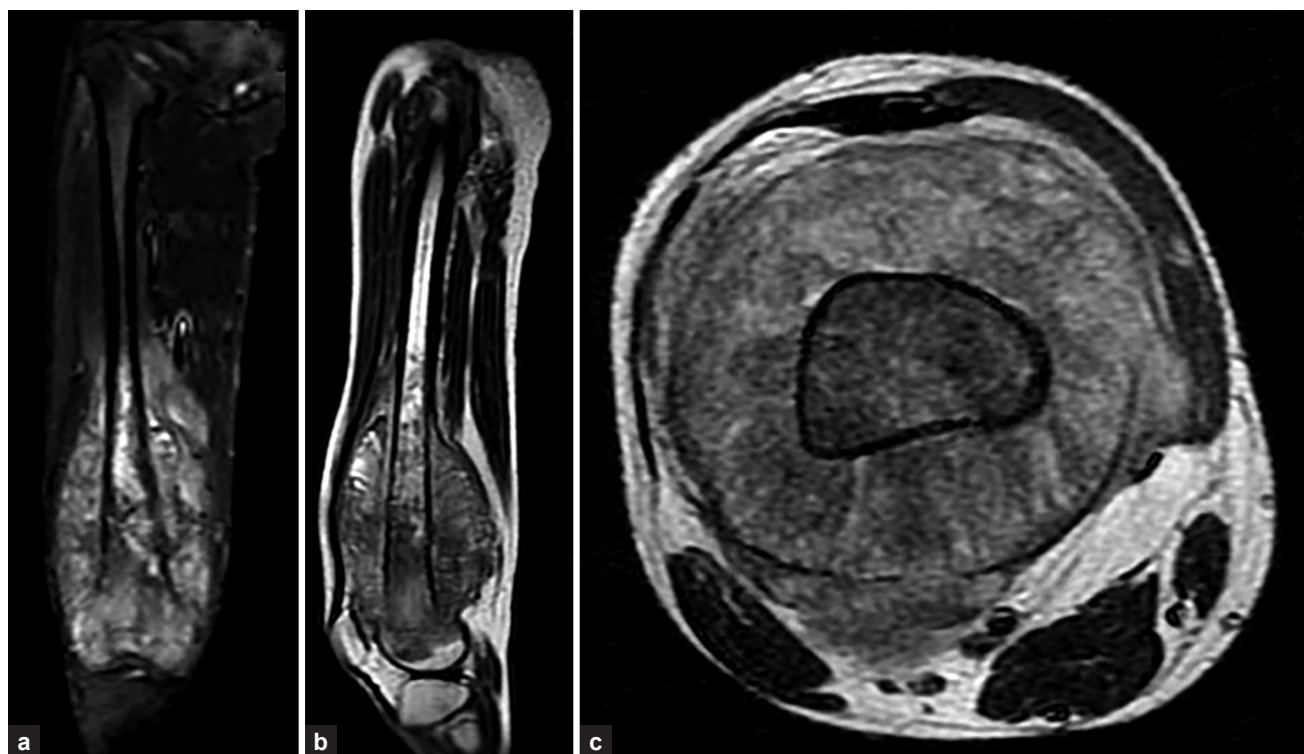
Figure 3B (a to c) Magnetic resonance imaging (MRI) of osteosarcoma distal end of femur. (a) T2-weighted coronal image; (b) T1-weighted sagittal image showing intramedullary extent and extraosseous soft tissue component without involvement of knee joint; (c) T2-weighted axial image showing large extraosseous component and free neurovascular bundle

TREATMENT

Malignant bone tumors are treated with a multidisciplinary approach and involve active participation from specialists from the medical, surgical and radiation oncology fields and would also need extensive input from the rehabilitation services as well. Most of the patients require a seamless coordinated interaction between the various treating disciplines. It is utmost important that all the components of the therapy are delivered at optimum time and in correct sequence. While adjuvant modality like chemotherapy is integral to management of both osteosarcoma and Ewing sarcoma, radiotherapy has limited role in the management of osteosarcoma. Overview of treatment is shown in **Box 1**.

Surgical Management

Surgery is an integral part in the management of malignant bone tumors. The surgical component of treatment mainly involves excision of tumor-bearing bone which can be achieved by ablative procedures like amputation or if suitable then with limb salvage. Limb salvage has two basic components, resection and reconstruction. The main principle of limb salvage lies in the fine balance of the two, which implies that resections procedure should be able to provide adequate disease clearance and the salvaged limb should be reconstructed in a manner that it should have better function than amputation and external prosthesis. The first and foremost goal of oncosurgery is to achieve complete disease clearance and reconstruction should always take a second place in the priority. The two main prerequisites for limb salvage are: (1) ability to achieve wide margin and (2) ability to reconstruct the limb in a way to provide better function than amputation. There are various contraindications for limb salvage. These mainly include, major vascular involvement; encasement of a major motor nerve;

Table 3 Tumor node metastasis (TNM) staging system proposed by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer. This staging system is based on histological grade, tumor size, presence or absence of regional lymph nodes and distant metastasis

T-Primary tumor		N-Regional lymph nodes		M-Distant metastasis	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M0	No distant metastasis
T1	Tumor 8 cm or less in greatest dimension	N1	Regional lymph node metastasis	M1	Distant metastasis
T2	Tumor more than 8 cm in greatest dimension			M1a	Lung
T3	Discontinuous tumors in the primary bone site			M1b	Other viscera and bone

poorly placed biopsy incisions; preoperative infection; intra-articular disease extension; nonunion of pathological fracture; or inadequate motor function.

After resection, the reconstruction can be done by number of biological and nonbiological methods. The choice of methods

Table 4 Stage grouping based on tumor node metastasis (TNM) staging and histological grade

Stage IA	T1	No	Mo	G1,2	Low grade
Stage IB	T2	No	Mo	G1,2	Low grade
Stage IIA	T1	No	Mo	G3,4	High grade
Stage IIB	T2	No	Mo	G3,4	High grade
Stage III	T3	No	Mo	Any G	
Stage IVA	Any T	No	Any M	Any G	
Stage IVB	Any T	N1	Any M	Any G	
	Any T	Any N	M1b	Any G	

Table 5 Options for reconstruction after tumor resection

- Nonbiological (megaprosthesis)
  - Standard megaprosthesis— used in mature skeleton
  - Expandable megaprosthesis—used in growing skeleton
- Biological
  - Allografts
  - Nonvascularized autografts
  - Vascularized autografts
  - Patients own sterilized tumor bone
  - Combination of allografts/sterilized tumor bone and vascularized auto grafts
  - Ilizarov
  - Rotationplasty

BOX 1 Overview of treatment in osteosarcoma and Ewing sarcoma

- Neoadjuvant chemotherapy followed by local therapy and adjuvant chemotherapy is the backbone of management of osteosarcoma and Ewing sarcoma
- The drugs most effective in osteosarcoma are cisplatin, doxorubicin and high-dose methotrexate
- Chemotherapeutic agents most effective in Ewing sarcoma are ifosfamide/cyclophosphamide, doxorubicin, vincristine, etoposide and actinomycin D
- Surgery is the main modality of local therapy for both primary and metastatic sites in osteosarcoma
- Ewing sarcoma is radiosensitive and hence radiotherapy is frequently used as the main modality of local treatment especially tumors of the axial skeleton which are frequently inoperable. This modality is also used for disease control at metastatic sites
- Effective management of side effects of chemotherapy, radiotherapy and surgical complications are the key to a successful outcome and hence treatment must be carried out at specialist centers equipped to handle these patients

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of reconstruction depends on number of factors like age of patient, type and site of tumor, affordability, needs of patient, infrastructure available and surgical expertise. A simplified list of options for reconstruction after limb salvage is shown in **Table 5**. The cases not suitable for limb salvage are treated with ablative surgery (amputation) or with definitive high dose radiation like in Ewing sarcoma. Radiotherapy is also the primary modality for unresectable Ewing sarcoma like in lesions of the spine, etc. Various sophisticated external prosthesis are available to provide reasonable function even after amputation surgeries.

Reconstruction of tumor defects in children is further more challenging due to number of factors like dynamic nature of growing bones, narrow medullary cavity, continually remodeling bone, greater functional demand and limb length discrepancy. Limb length discrepancy is a major problem in lower limb especially in lower limbs. This can be addressed by a number of factors, which include, use of expandable prosthesis (minimally invasive or noninvasive), vascularized epiphyseal transfers or by Ilizarov lengthening at a later stage. Rotationplasty can also be an option in very young patients and where affordability of expendable prosthesis is the issue. Rotationplasty ensures that the opposite knee and the repositioned rotated ankle of the operated limb lie at the same level at skeletal maturity and provide much better function as compared to amputation.

Chemotherapy

Chemotherapy is always indicated for the malignant bone tumors—osteosarcoma and Ewing sarcoma. It should be clearly understood that even when nonmetastatic, both these malignancies are considered as systemic diseases and without

systemic chemotherapy, more than 80% of patients will develop metastases and not survive. The current standard of care in chemotherapy management of osteosarcoma constitutes 3–4 cycles of neoadjuvant chemotherapy (presurgery chemotherapy) followed by local therapy (surgery) and this is followed by 3–4 cycles of adjuvant chemotherapy (postsurgery chemotherapy). Resection of all metastatic lesions, if possible is included in the local therapy. The *back bone* of chemotherapy regimen for osteosarcoma is formed by cisplatin, doxorubicin and high dose methotrexate which are the most effective drugs used in the management. Other active first-line chemotherapeutic drugs are ifosfamide and etoposide. Various regimen use different combinations of the earlier drugs to constitute the neoadjuvant and adjuvant chemotherapy cycles. The combination of cisplatin and doxorubicin with high dose methotrexate, with or without addition of ifosfamide and etoposide has been evaluated in many clinical trials with equivocal survival rates and toxicities. The logistics of administering high dose methotrexate with adequate hydration and alkalinization, along with facilities to monitor drug levels at multiple time intervals, are difficult and may not be available at smaller centers.

The management of Ewing sarcoma is similar to that of osteosarcoma but with a better-defined role of radiotherapy. Whereas osteosarcoma is conventionally considered radio-resistant, Ewing sarcoma cells are more sensitive to radiotherapy. The standard treatment regimes constitute 12–16 weeks of neoadjuvant chemotherapy followed by local therapy and then an additional 28–32 weeks of adjuvant chemotherapy. The most active chemotherapy drugs for Ewing sarcoma are doxorubicin, ifosfamide, cyclophosphamide, etoposide, vincristine and actinomycin-D. The early dose intensity of doxorubicin in treatment of Ewing sarcoma has shown increased complete pathological responses and improved survival. The role of high dose chemotherapy (with autologous hematopoietic stem cell transplant) is yet to be proven and hence is not advocated other than in a clinical trial setting.

Chemotherapy management of malignant bone tumors in children can result in significant toxicity requiring frequent hospital visits or admissions for supportive care. Commonly encountered side effects are infections (febrile neutropenia), vomiting, gastrointestinal disturbances (including mucositis, diarrheal disorder and constipation), electrolyte disturbances, liver dysfunction (mainly elevated liver enzymes), neuropathic pain, central neurotoxicity, etc., and these children frequently need transfusion support (red cells and platelets). Although the earlier toxicities of therapy are short lived, children also need to be closely monitored (during therapy) for dose limiting toxicities and post-treatment late effects such as cardiotoxicity (due to doxorubicin), nephrotoxicity (due to cisplatin, ifosfamide) and ototoxicity (cisplatin induced). Uncommon late effects of therapy

include infertility and second malignancies. All children treated with chemotherapy would need long-term surveillance to monitor for late effects and disease recurrence.

Radiotherapy

The role of radiotherapy is well defined for management of Ewing sarcoma and has no clear benefit in the management of osteosarcoma. Although there is no study which has looked at a *head to head* comparison between radiotherapy and surgery in local management of Ewing sarcoma, it is generally perceived to be equally effective. However, conventionally surgery is preferred over radiotherapy in local management of Ewing sarcoma especially if tumor is located in the limbs where complete surgical excision is frequently feasible. Radiotherapy is the main modality of local therapy in Ewing sarcoma of the axial skeleton (vertebra, pelvic bones, and skull bones) where adequate surgical clearance is unlikely. It must be emphasized that there is no role for *debulking* surgery where only partial resection of the tumor is feasible. In such situations the primary mode of local therapy should be radiotherapy. Radiotherapy following surgery is indicated when histological response (necrosis) of the tumor to neoadjuvant chemotherapy is inadequate, if there is any tumor spillage or rupture during surgery or if surgical margins are positive on histopathology. The dose of radiation administered for local control of primary tumor is usually 55.8 Gy in fractionated doses to prechemotherapy tumor volume. Definitive or palliative radiotherapy is also indicated in metastatic disease. Whole lung radiotherapy is indicated in patients who have had pulmonary metastases of Ewing sarcoma. Radiotherapy to other metastatic sites could also be considered based on the number of sites that need to be irradiated.

PROGNOSTIC FACTORS

Age, metastasis at presentation and response to neoadjuvant chemotherapy are the most important prognostic factors for both osteosarcoma and Ewing sarcoma. Older age of presentation (> 15 years), presence of metastasis at initial presentation and poor response to neoadjuvant chemotherapy, portends poor outcome for both these malignancies. Patients with less than 90% tumor necrosis, or in other words, patients with more than 10% viable tumor after neoadjuvant chemotherapy, at the time of surgical histopathology evaluation, have much poorer survival as compared to patients with more than 90% tumor necrosis. The site of metastasis also has prognostic implication where in children with metastasis to lungs do better compared to patients who have metastasis to bone and/or bone marrow sites. Additionally, the commonly seen translocation in Ewing sarcoma (EWS-FLI1) although diagnostic has not been shown to be of prognostic significance. The 5-year survival outcomes for nonmetastatic osteosarcoma and Ewing sarcoma is expected to be in the range of 60–70%. Outcome for metastatic disease is much poorer with 5-year survival ranging from 20% to 40%.

IN A NUTSHELL

1. Osteosarcoma followed by Ewing sarcoma are the most common malignant bone tumors seen in children and adolescents.
2. The most common site of occurrence of osteosarcoma is around the knee joint. Ewing sarcoma can affect both the axial and appendicular skeleton.
3. Diagnosis of these tumors requires a thorough clinicoradiological approach substantiated by robust histopathological confirmation.
4. Approximately 25% of the tumors are metastatic at presentation and metastatic disease portends a poor outcome. Therapy should only be initiated after complete workup for metastatic disease.
5. Systematic multidisciplinary approach to management is the mainstay of therapy of these tumors. The long-term cure rates for localized disease are 60–70% and 20–40% for metastatic disease.
6. In osteosarcoma surgery and multiagent chemotherapy are the main modalities of therapy. Radiotherapy has limited role.
7. In Ewing sarcoma, the multimodality therapy includes surgery, radiotherapy and multiagent chemotherapy.
8. Contemporary surgery and the advent of megaprosthesis has now made limb salvage much more feasible in the present day. With the advent of multimodality treatment the need for ablative surgery (amputation) has substantially decreased.
9. Treatment of these tumors must be taken up only at specialist centers which have the expertise and infrastructure to manage these children effectively.
10. Children treated for these tumors need lifelong surveillance for late effects.

MORE ON THIS TOPIC

Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol. 2010;11:184-92.

Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. Oncologist. 2006;11:503-19.

Biermann JS, Adkins DR, Agulni KM, et al. Bone cancer. J Natl Compr Canc Netw. 2013;8:688-723.

Gorlick R, Bielack S, Teot L, et al. Osteosarcoma: biology, diagnosis, treatment and remaining challenges. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams Wilkins; 2011. pp. 1015-45.

Hawkins DS, Bolling T, Dubois S, et al. Ewing sarcoma. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams Wilkins; 2011. pp. 987-1015.

Jaffe N, Puri A, Gelderblom H. Osteosarcoma: evolution of treatment paradigms. Sarcoma. 2013;2013:203531.

Lu Y, Villalobos C, Zamora R, et al. Radiographic and scintigraphic evaluation of bone tumors and diseases. JBJS Reviews. 2014;2:e5

Luetke A, Meyers PA, Lewis I, Juergens H. Osteosarcoma treatment: where do we stand? A state of the art review. Cancer Treat Rev. 2014;40:523-32.

Chapter 45.15
Oncological Emergencies and Supportive Care
Anand Prakash, ATK Rau

An oncological emergency may be defined as any life-threatening condition which may arise as a result of the oncological disease or at any time during therapy for the same. Children with malignancies can present with emergencies associated with various organ systems and the early recognition and appropriate management of these emergencies will save lives. Children with cancer can present with these conditions either at diagnosis or at any stage of therapy. A significant component of pediatric oncological care deals with the aggressive management of oncological emergencies and efficient supportive care. This aspect is indeed so vital that improvements in supportive care alone have led to vastly improved outcomes in pediatric cancers worldwide. This is especially true in the developing world. The common oncological emergencies and supportive care are as shown in **Box 1**.

BOX 1 Common oncological emergencies and supportive care aspects

- Oncological emergencies:
  – Infections and febrile neutropenia
  – Tumor lysis syndrome
  – Superior mediastinal and vena caval syndromes
  – Spinal invasion of tumors
- Supportive care aspects:
  – Blood component therapy
  – Nutrition care
  – Colony stimulating factors
  – Immunization
  – Pain management

INFECTIONS AND FEBRILE NEUTROPENIA

Prompt recognition of infections, early initiation of antimicrobials and intensive monitoring significantly decreases the morbidity and mortality in this condition. The first section deals with the reasons why a child with cancer is prone for infections. The second section deals with the care of the febrile neutropenic child which is the most common and important aspect of pediatric cancer supportive care.

Infections in Children with Cancer

Both innate and adaptive immunity are disturbed in the pediatric oncology patient as discussed in the following sections; and they are more predisposed to infections compared to other children.

The Mucocutaneous Barrier

The skin and mucous membranes provide the first line of defense against microbes. Disruptions in the skin and mucosa in these patients is multifactorial in origin and can be caused by chemotherapy (leading to mucositis), surgery and radiotherapy. Important chemotherapeutic drugs causing mucositis include cytarabine, methotrexate, anthracyclines and etoposide especially when given in high doses. Additionally, central venous access devices and common procedures like feeding tubes, urinary catheters, venipunctures and bone marrow aspiration all breach the skin or mucosal barrier and are portals for bacterial invasion.

Phagocytic Cells

Polymorphonuclear cells, monocytes and macrophages are the innate phagocytic cells. Neutrophils play a key role in the host defense against both bacteria and fungi. The absolute number and functioning of neutrophils are both affected during cancer chemotherapy. The patient may be neutropenic either because of the disease (e.g., marrow infiltration by leukemia) or marrow suppression following chemotherapy. Three key factors determine the risk of febrile neutropenia in a patient: (1) the severity of neutropenia (2) rate of fall of absolute neutrophil count (ANC) and (3) the duration of neutropenia. Any neutropenia with an ANC of less than 500 lasting more than 7 days markedly increases the risk of sepsis.

Adaptive Immunity

Both T-cell and B-cell related immune mechanisms are affected during cancer chemotherapy. The Herpes group of viruses and *Pneumocystis* are two important opportunistic pathogens due to suppressed adaptive immunity.

Malnutrition

It is an important contributor to immunodeficiency and is a major factor in the tolerance of these children to chemotherapy in developing countries.

Febrile Neutropenia

Febrile neutropenia is of great importance in the pediatric oncology unit because of its commonality and the need for early recognition and aggressive management. Infections in neutropenic patients can be potentially life-threatening and patients commonly present with fever without a definite focus and may deteriorate rapidly while awaiting body fluid culture results. Thus, patients with febrile neutropenia must be administered the first dose of antibiotic in the emergency room itself. Fever may be the only sign of infection in a neutropenic patient and because of low neutrophil counts itself, may not be very significant. There may also be other reasons for the fever such as the disease process itself (e.g., acute lymphoblastic leukemia [ALL]), blood product transfusions, allergic reactions and chemotherapeutic drugs (e.g., bleomycin and cytosine arabinoside). However, any fever in a neutropenic patient is considered significant and warrants prompt evaluation and initiation of antibiotics. An ANC of less than 500/mL is a very significant risk for febrile neutropenia while an ANC of less than 1,000 which is likely to fall below 500 in the next few days is also included in this group. **Table 1** details the common organisms isolated in febrile neutropenia.

Table 1 Common organisms in febrile neutropenia

- Gram-negative
  – *Pseudomonas*
  – *Klebsiella*
  – *E. coli*
  – Enterococci
  – *Serratia*
- Gram-positive
  – *Staphylococcus aureus*
  – *Streptococcus*
- Anaerobes
- Fungi
  – *Candida spp.*
  – *Aspergillus*
- Viruses
  – Herpes simplex and zoster
  – Cytomegalovirus

Table 2 Risk stratification in febrile neutropenia

High risk: If any of the following are present
• Acute leukemia not in remission
• Hemodynamic instability or comorbidity
• Prolonged severe neutropenia (ANC < 100 cells/mL) or duration > 7 days. Pneumonia or other focus of infection at time of presentation
• Severe mucositis (Grade 3–4)
• Hepatic or renal insufficiency
• Altered sensorium
Low risk:
• Solid tumors and leukemias in remission
• No comorbidities or focus of infection
• ANC > 100/mL and Short duration (< 7 days) of severe neutropenia
• No hepatic or renal insufficiency

Abbreviation: ANC, absolute neutrophil count.

Evaluation of the Febrile Neutropenic Patient

A careful history and meticulous clinical examination is required. **Table 2** describes the relevant history and clinical examination in this setting. The blood counts and culture are the key investigations in a febrile neutropenic patient. The blood count gives us a serial monitor of the ANC and allows us to decide if the patient is recovering from the neutropenia. It also helps decide packed cell and platelet transfusions requirements during the therapy. BACTEC and other rapid culture detection systems are preferred. Blood should be drawn for culture before the antibiotic dose and must be of adequate volume. Where intravenous (IV) devices are in situ, it is important to draw cultures from each of the ports. Other investigations usually required include a urine culture in young children, chest imaging if symptomatic and if clinically indicated, stool evaluation. Once the blood cultures are drawn, the first dose of IV antibiotics is immediately given. The rapidity with which antibiotics are administered after the onset of fever has been shown to correlate with mortality in febrile neutropenia.

Evaluation of a Febrile Neutropenic Child

Many children as part of their chemotherapy receive steroids which may mask fever. In such patients, in the presence of neutropenia even minor complaints like abdominal pain may need to be taken seriously. It may be the first signs of intestinal inflammation (typhlitis). Redness and pain along a central venous access device may indicate infection even in the absence of fever. In these situations, it is often prudent to immediately draw blood cultures and start antibiotics rather than adopt a wait and watch policy.

Risk Stratification for Treatment of Febrile Neutropenia

Traditionally, all febrile neutropenia patients were admitted and treated with IV antibiotics. The approach has now evolved into the risk grouping of patients into *high* and *low* risk groups to decide whether admission is required. **Table 3** describes the common factors deciding the risk stratification in febrile neutropenia. Every oncology unit should develop guidelines to decide which patients would receive outpatient therapy for febrile neutropenia.

Care of the Febrile Non-neutropenic Child

Like in the neutropenic child, blood cultures need to be drawn. However, if the child is clinically well, immediate antibiotic therapy is not necessary. Only for the patients with an indwelling central venous access device, a single broad spectrum antibiotic is started pending blood cultures as the risk of catheter related bloodstream infection is significantly higher than other children.

Antimicrobial Therapy for Febrile Neutropenia

The choice of antibacterial for empirical therapy in febrile neutropenia is determined by the common organisms isolated

Table 3 Clinical evaluation and work-up in febrile neutropenia

History:
• Duration of fever
• Presence of rigors
• Symptoms to suggest focus of fever
– *Respiratory*: Cough, chest pain, rapid respiration/ breathlessness
– *GIT*: Abdominal pain, vomiting, loose stools, melena, hematochezia
– *Other focus*: Mouth ulcers, skin infections, perianal pain
Clinical examination:
• Vital signs and general condition
– Important to rapidly recognize hemodynamic compromise due to septic shock
• Review of foci of infection/complications of neutropenia
– Oral cavity for mucositis/candida/patch on the tonsils or pharynx/ dental infections
– *Skin*: Pyoderma, petechiae, thrombophlebitis, central venous line/ port site infections
– *Chest*: Signs of lower respiratory infection (especially assess for signs of hypoxia with minimal chest findings suggestive of PCP or viral pneumonias)
– *Abdomen*: Distension, mass, free fluid, tenderness (suggestive of neutropenic enterocolitis); perianal exam for anal fissures/abscess
Other factors determining the therapy plan:
• *Type of cancer*: Hematolymphoid malignancy versus solid tumor
• *Disease status*: Active disease versus in remission
• *Phase of treatment*: On intensive chemotherapy versus maintenance

Abbreviations: GIT, gastrointestinal tract; PCP, *Pneumocystis carinii* pneumonia.

in that institution and susceptibility profiles. The drug should have a wide spectrum of coverage for both gram-positive and negative organisms, be bactericidal, and as nontoxic and easy to administer as possible. This has conventionally involved the use of two antibiotics which increases coverage and provides synergistic action at the lowest possible minimum inhibitory concentration (MIC). The traditional two drug combination includes a third generation cephalosporin and an aminoglycoside. Fourth generation cephalosporins and carbapenems provide an alternative as single drug regimens in the first line of empirical therapy.

A febrile neutropenic patient needs careful monitoring of respiratory and hemodynamic status. Septic shock if picked up early and appropriately managed has as good an outcome as children without cancer. By 48–72 hours of initiation of the first line of antibiotics, if the patient is still febrile, a detailed reassessment to modify antimicrobial therapy is required. Based on the initial blood culture reports, a decision to initiate enhanced gram-positive (specifically antistaphylococcal) cover with glycopeptides such as vancomycin needs to be taken. By day 5–7, if the patient continues to be febrile and neutropenic, empirical antifungal therapy with amphotericin B or caspofungin is warranted.

In certain clinical situations, a gram-positive cover with vancomycin is preferred upfront. These include a child with a central venous access device related infection, the presence of severe mucositis especially after acute myeloid leukemia (AML) therapy with high dose cytarabine or a focus of infection in the skin or lung. In these settings, severe gram-positive sepsis, especially with *Staphylococcus aureus* or *Streptococcus viridans* is of tremendous concern. In addition, if a neutopenic child at initial presentation presents with shock, vancomycin may be started as part of the initial therapy and antibiotics later changed based on blood culture sensitivity reports.

The close monitoring with clinical evaluation for new symptoms, signs of hemodynamic compromise and repeat blood counts and blood cultures help in taking decisions on modification of antimicrobial therapy. Persistence of fever in a neutropenic child and evidence of shock are indications to repeat blood cultures

and modify antibiotic therapy (e.g., change from ceftazidime and amikacin to beta lactam-beta lactamase inhibitor combination with aminoglycosides or carbapenems). Based on previous culture reports, each oncology unit will develop its own antibiotic protocols. As prolonged neutropenia predisposes to fungal infections, and proving a fungal infection with the current available microbiological and imaging investigations is difficult, empirical therapy with antifungals is initiated to save lives in children with persistent fever. The duration of expected neutropenia is also important as this also determines how aggressive the therapy needs to be, e.g., febrile neutropenia during ALL or AML induction therapy carries a more ominous outcome when compared to a child with a solid tumor in remission. Many children with hematolymphoid malignancies may need packed cell or platelet support during therapy for febrile neutropenia. Based on the recovery from both fever and neutropenia, decisions can be taken regarding the possibility of discharge and oral antibiotic therapy at home. **Flow chart 1** provides an algorithm for management of febrile neutropenia.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is a group of metabolic abnormalities that occur due to the rapid release of intracellular substances from tumor cells. Hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia are the main metabolic derangements seen in TLS. Rapid and severe derangements in these biochemical parameters may lead to acute kidney injury (AKI) with a sudden and dramatic fall in the glomerular filtration rate (GFR). These biochemical changes may also lead to arrhythmias, seizures and death in some cases.

TLS usually occurs within 12–72 hours of initiation of chemotherapy. In some tumors, it may occur spontaneously when the patient presents with renal dysfunction at the time of diagnosis. Certain important variables determine whether TLS will occur in a particular child or not and its severity. Tumors, which have a high proliferative rate (e.g., Burkitt lymphoma), have a high tumor burden and those highly sensitive to chemotherapy are prone to develop TLS.

Definition

Tumor lysis syndrome can be defined in terms of derangement in metabolic parameters (laboratory TLS) or in terms of clinical features (clinical TLS). Early detection of laboratory TLS helps in the correction of metabolic parameters and the prevention of the clinical features of TLS. **Table 4** describes the definitions for TLS. Clinical features of TLS may include nausea, vomiting, diarrhea, anorexia, fluid overload, hematuria, congestive heart failure, lethargy, edema, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death.

The risk factors for development of TLS are listed in **Table 5**. Based on the earlier risk factors, a child can be risk stratified into having a high, intermediate or low risk of having TLS and its complications. The risk stratification helps to plan therapeutic interventions to prevent the complications of TLS.

Sequence of Events in Tumor Lysis Syndrome and Pathophysiology of Acute Kidney Injury

Tumor cells contain large quantities of uric acid, a metabolite released from the breakdown of nucleic acids (purines and pyrimidines). As tumor cells lyse either due to chemotherapy or spontaneously, blood levels of uric acid rise. In the initial stages, elevated uric acid levels may cause a drop in the GFR due to the formation of uric acid crystals. Cell lysis also leads to elevation of serum potassium while the decrease in the GFR contributes to the elevation of serum phosphate (also an intracellular substance from cancer cells). The elevated phosphate causes a consequent decrease in serum calcium as the body homeostasis attempts to maintain a normal calcium-phosphate product. The altered calcium and phosphate levels contribute to the deposition of calcium phosphate crystals in the tubules which further worsens renal function. The sudden elevation of serum potassium can precipitate life-threatening arrhythmias while low calcium levels may cause seizures. Both the elevated uric acid and elevated phosphate levels contribute to the decrease in the GFR resulting in oliguria and renal shutdown. This vicious cycle of decreased GFR contributing to further electrolyte disturbance and further drop in GFR leads to the laboratory and later the manifest clinical features of TLS.

Management

When chemotherapy is initiated for a malignancy, tumor lysis must occur for cure. However, the cardinal principle of management is to prevent the abnormal metabolic parameters from causing severe derangement of kidney function leading to AKI. Early recognition of the risk of TLS allows for prevention of major metabolic changes and to obviate the need for renal replacement therapy. Pre-existing renal dysfunction, dehydration, acidic urine, oliguria and rarely primary involvement of the kidneys by the malignancy all contribute to TLS. The management of TLS is described in **Table 6**.

Indications for Dialysis

Indications for the start-up of renal replacement therapy in TLS include persistent hyperkalemia, severe metabolic acidosis, volume overload unresponsive to diuretic therapy, and overt uremic symptoms, including pericarditis and severe encephalopathy. Dialysis may be initiated *prophylactically* before the development of overt uremic symptoms in response to severe, progressive hyperphosphatemia (> 6 mg/dL) or severe symptomatic hypocalcemia. The appropriate timing for dialysis remains unresolved. Frequent (daily) dialyses are recommended considering the continuous release into the bloodstream of purine-products, potassium, electrolytes and other metabolites from lysed tumor cells.

SUPERIOR VENA CAVA SYNDROME AND SUPERIOR MEDIASTINAL SYNDROME

Many malignancies in children present with thoracic masses which will cause respiratory distress. If the thoracic mass compresses the superior vena cava, it is termed superior vena cava syndrome (SVCS) and if there is tracheoesophageal compression, it is called the superior mediastinal syndrome (SMS). The common clinical features of a thoracic mass include respiratory distress, orthopnea, facial flushing and tachycardia. Cough, hoarseness and change in voice may also develop. Vascular stasis may cause headache and blurring of vision. All symptoms worsen in the supine position and the child prefers to sit up. Edema of the face and limbs, cyanosis and dilated superficial veins may also be seen. Progressive worsening can lead to drowsiness and respiratory failure due to hypoxia and hypercarbia. While the most common cause of SVCS is a malignant mediastinal mass, cardiovascular surgery or central venous lines leading to SVC thrombosis, mediastinal granulomas and infections like histoplasmosis can also cause SVCS. The common causes of SVC syndrome in children are listed in **Table 7**. Some of these tumors will be associated with pleural and/ or pericardial effusions. The presence of these effusions also contributes to the severity of respiratory distress.

Flow chart 1 Algorithm for management of fever in a child with cancer

• Fever 38°C/100.4°F twice in 1 hour or temperature > 38.5°C/101.5°F
• ANC < 500 or < 1000 per mm^3 and falling
• Do not administer acetaminophen alone without further assessment

Immediate Steps:

• Assess general condition and vitals for hemodynamic compromise
• Send CBC, blood culture; consider urine exam, RFT, serum electrolytes,CXR if needed
• Send blood cultures from vascular access device if present
• Start first line broad spectrum antibiotic (single/dual) immediately
• Assess need for upfront vancomycin
  – Presentation with shock
  – Signs of central venous access device infection (redness, pain)
  – Severe mucositis (e.g., following AML chemotherapy)
• If hypotensive treat as septic shock
  – Consider adding aminoglycoside or Vancomycin
• Contact oncology unit to decide on:
  – GCSF support
  – Continuation or withhold of current chemotherapy
  – Specific concerns like previous cultures and infections (e.g., fungal) that have been positive

Admit to ward where close monitoring possible

• Assess hemodynamic and respiratory status every 2–4 hours especially first 24 hours of admission
• Monitor for signs of septic shock
• Decide on supportive blood product use
• Maintain good hydration, if required by IV fluids

Daily assessment:
• Fever pattern
• Blood counts
• Blood cultures (if febrile)
• General condition
• Onset of new symptoms

• Fever absent or downward trend
• Improving ANC
• Blood cultures negative/growth of sensitive
  organism
• General condition stable

• Fever present/increasing ± rigors
• Blood cultures negative
• Toxic/hemodynamic compromise

• Continue first line antibiotics
  till 48 hours afebrile, ANC recovers to > 500
                OR
• Appropriate duration for infection/organism
  in a proven focus

• Fever persistent for 3 days
• Blood cultures negative
• General condition stable

• Repeat blood culture
• Start 2nd line/3rd line antibiotics (e.g.,
  piperacillin-tazobactam/cefoperazone-
  sulbactam/meropenem) ± aminoglycoside
• GCSF in consultation with oncology unit

• Consider adding gram-positive
  cover, e.g., vancomycin

• Fever absent or downward trend
• Improving ANC
• Blood cultures negative/growth of sensitive organism
• General condition stable

• Fever persisting for 5–7 days
• Blood cultures negative
• General condition stable

 • Continue antibiotics till afebrile and ANC > 500

Evaluate and treat for fungal infection
• Blood cultures for fungal growth
• Consider CT chest/sinuses for *Aspergillus* infection
• Abdominal ultrasound for hepatosplenic candidiasis
• Empirical Amphotericin B to be started
• Modify antifungal based on evaluation for fungal infection

• Continue antibiotics and antifungals till afebrile with ANC > 500 and rising and general condition stable

Abbreviations: ANC, absolute neutrophil count; CXR, chest X-ray; CBC, complete blood count; GCSF, granulocyte colony stimulating factor; AML, acute myeloid leukemia; CT, computed tomography; RFT, renal function test.

Table 4 Tumor lysis syndrome (TLS) definition: Laboratory and clinical TLS

Laboratory tumor lysis syndrome: Cairo-Bishop definition		
Parameter	Value	Change from baseline
Uric acid	≥ 8 mg/dL	25% increase
Potassium	≥ 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease
Two or more changes defines TLS and usually occurs within 3 days before or 7 days after chemotherapy		
Clinical criteria: Presence of laboratory TLS and either of the following:		
• Cardiac arrhythmia • Seizure • Death		

Table 5 Factors associated with risk of development of tumor lysis syndrome

1. *Tumor type*: Rapidly proliferating and highly chemosensitive tumors
   A. Burkitt lymphoma
   B. Lymphoblastic lymphoma
   C. Acute lymphoblastic leukemia

2. Tumor size and extent:
   A. Large tumors > 10 cm
   B. Elevated LDH > twice the upper limit of normal
   C. High WBC count > 50,000 per mm^3
   D. Large liver/spleen/mediastinal mass/lymph nodes

3. Baseline renal function:
   A. Renal compromise at presentation: Dehydration

4. Baseline uric acid:
   A. Baseline uric acid > 7.5 mg/dL

Table 6 Principles of tumor lysis syndrome (TLS) treatment

• Hydration (potassium free fluids) at 3 L/m^2/day to ensure urine output of 80–100 mL/m^2/hour

• Allopurinol 100 mg/m^2/dose q8h

• Furosemide may be added to ensure adequate urine output

• Monitoring of BUN, serum creatinine, uric acid, serum calcium, serum phosphate, serum potassium at regular intervals, frequency depending on the risk and severity of tumor lysis

• Rasburicase (0.1–0.2 mg/kg) for one dose especially in high risk cases

• *Hyperkalemia*: Treat as per protocol

• *Hyperphosphatemia*: Phosphate binders, dialysis

• *Hypocalcemia*: Asymptomatic—no therapy; symptomatic—IV calcium gluconate

Abbreviation: BUN, blood urea nitrogen.

Management

As the SVC is a thin walled vessel with low pressure, it is easily compressed. Lymph node and thymic enlargement or infection results in compression and thrombosis of the SVC leading to stasis. In infants and toddlers, the trachea and bronchi being much smaller in size are more easily compressible. Hence, the symptoms of tracheal compression are more common in younger children.

The evaluation and management of SVC syndrome is listed in **Table 8**. Assessment of the airway, oxygen supplementation and correction of hemodynamic compromise is the first step. Imaging, with posterior-anterior and lateral views will help in the assessment

Table 7 Causes of superior vena cava (SVC) syndrome

• Tumors
  – Lymphoblastic lymphoma (T-NHL)
  – T-cell acute lymphoblastic leukemia
  – Hodgkin lymphoma
  – Germ cell tumors
  – Thoracic neuroblastoma
  – Thymic tumors

• Other causes
  – Tuberculosis
  – Sarcoidosis
  – SVC clot due to central venous access
  – Behçets syndrome

Table 8 Evaluation and treatment of superior vena cava (SVC) syndrome

Principle of treatment: Make diagnosis with least invasive test possible and treat urgently

• CT chest in prone position
• Complete blood count with peripheral smear to assess for blasts
• Tap pleural/pericardial effusion and assess for malignant cells; flow cytometry can also be done on these fluids
• Bone marrow aspiration in lateral position
• CT-guided biopsy of mass if any of the earlier options are not feasible under local anesthesia
• Admit to PICU, avoid any sedatives
• Prop up and lateral position, monitor vitals especially respiratory distress, supplement oxygen
• Therapy may need to be empirical if no tissue diagnosis possible and patient in distress
• Steroid therapy (dexamethasone/prednisolone) causes rapid improvement in NHL, T-ALL, HL
• Radiotherapy is considered if no response to the above
• Surgical excision considered if evaluation suggestive of solid tumor, e.g., germ cell tumor, sarcoma

Abbreviations: CT, computed tomography; PICU, pediatric intensive care unit; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia.

of the size and extent of the mass **(Figures 1A and B)**. A computed tomography (CT)-chest is very useful in assessing the degree of airway compromise and also in assessing vascular compression. The CT may also be helpful in assessing the type of tumor and its spread into the adjacent tissues. While nodes are usually uniform in nature, germ cell tumors with its solid and cystic appearance may reveal a heterogeneous picture. Noninvasive tests include tumor markers like the beta human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) for germ cell tumors and urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) for neuroblastoma which will also be helpful in deciding the further line of management.

HYPERLEUKOCYTOSIS

The definition of hyperleukocytosis is a peripheral white blood cell (WBC) count of more than 100×10^9/L. This high white cell count usually occurs in ALL, AML or chronic myeloid leukemia (CML). Infants with leukemia, T cell ALL, the blast phase of CML and the MLL gene are all associated with hyperleukocytosis. The high white cell count causes increased viscosity and sludging in the circulation due to malignant cell aggregates and thrombi. Additionally, an increased adhesive interaction between blasts and damaged endothelium also contributes to the slowing of circulation resulting in the various symptoms encountered in this condition. As myeloid blasts are larger than lymphoid blasts, children with AML are more
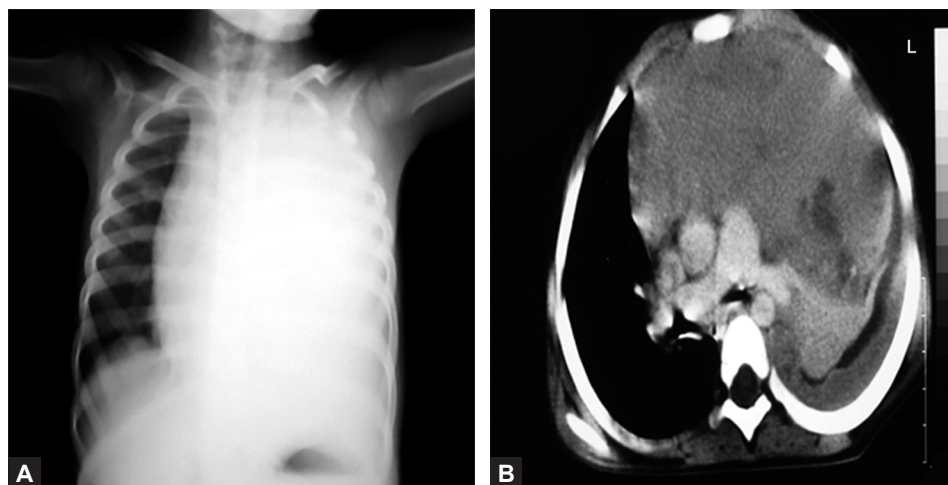
Figures 1A and B Chest X-ray (A) and computed tomography (CT) scan (B) of child with a mediastinal mass due to T-lymphoblastic lymphoma. Note the minimal pleural effusion in the left hemithorax

prone for the complications of hyperleukocytosis. High WBC counts in association with AML may also precipitate disseminated intravascular coagulation (DIC), hence adequate fresh frozen plasma and platelet support may be warranted during therapy.

Most children with high white cell counts will be asymptomatic. CNS symptoms include altered sensorium, seizures, headache, blurred vision, stroke and papilledema. Pulmonary symptoms include dyspnea, cyanosis, hypoxia and pulmonary bleeding. Rarely priapism and dactylitis may be seen. The management of a child with hyperleukocytosis is depicted in **Table 9**.

SPINAL CORD COMPRESSION

This oncological emergency occurs in various tumors arising either from the spinal cord or from structures surrounding the cord like the vertebral bodies. Masses arising from the spinal cord, conus medullaris or cauda equina need rapid therapy to decrease long-term neurological deficits. Common tumors in the spinal cord are listed in **Table 10**. Compression of the vertebral venous plexus results in venous hemorrhage, ischemia and vasogenic cord edema. Vertebral body involvement with secondary compression of the cord can occur in children but is more common in adults. The symptoms depend on the anatomical location, extent of invasion and the origin of the mass. Tumors that are extradural present with radicular *root* pains as the first symptom. Radicular pain is classically more at night when the child lies down. In contrast, intradural, intramedullary tumors may present with bladder or bowel symptoms first before causing any other symptom. The level of maximal spinal tenderness is a good localizing sign to determine the level of spinal compression. It is important to note that absence of motor, sensory or sphincter deficits does not rule out spinal involvement. Many children have a persistent backache for many months prior to diagnosis. Neurological symptoms like paraplegia and quadriplegia, occur late in the illness but progress rapidly and may cause irreversible deficits.

Magnetic resonance imaging (MRI) imaging with contrast is the investigation of choice **(Figure 2)**. X-rays and bone scans are much less sensitive and not reliable in this setting. Based on the suspected diagnosis, an imaging guided biopsy is required and therapeutic decisions are taken based on the biopsy. Dexamethasone is the initial treatment of choice. It reduces vasogenic edema and improves neurological outcome. A loading

Table 9 Hyperleukocytosis management

• Ensure adequate hydration and start supportive therapy as per tumor lyses syndrome protocol • Monitor for respiratory distress, sensorium changes, urine output
Specific therapy:
• *In ALL*: Therapy with steroids (as part of induction)   *In AML*: Hydroxyurea along with induction chemotherapy • Leukapheresis in selected cases with organ dysfunction or priapism

Abbreviations: ALL, T-cell acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Table 10 Causes of spinal cord compression

• Extradural
  – Metastatic cancers
  – Schwannomas

• Intradural-extramedullary
  – Meningiomas
  – Neurofibromas
  – Ependymomas

• Intramedullary   – Astrocytomas

• Vertebral body involvement
  – Metastatic neuroblastoma
  – Metastatic Ewings
  – Langerhans cell histiocytosis
  – Leukemia/lymphoma (NHL)

Abbreviation: NHL, non-Hodgkin lymphoma.

dose of 1.0–2.0 mg/kg followed by 0.25–0.5 mg/kg every 6 hours is the usual schedule. Surgery, radiotherapy and chemotherapy all have a role in the therapy of spinal compression. Since most pediatric tumors are chemosensitive like lymphomas, leukemias, Ewing sarcoma, neuroblastoma, etc., emergency chemotherapy along with steroids usually causes a dramatic reduction in tumor size and symptoms. In case of poor response to chemotherapy, radiotherapy is the treatment of choice in radioresponsive tumors. Doses of 200–800 cGy are usually administered along with dexamethasone. Radiotherapy is avoided in children younger

Figure 2 Spinal tumor (Non-Hodgkin lymphoma) with vertebral compression fracture of vertebral body and bilateral enlargement of the kidneys

than 3 years of age. Surgery is considered in chemotherapy and radiation resistant tumors or in children with rapidly progressing paraparesis on chemotherapy and usually includes laminectomy and decompression.

Long-term prognosis is based on the degree of deficits at presentation. Residual deficits are based on the degree of invasion of the tumor. Up to 50% of children who are paraplegic at the time of presentation regain their ability to walk after initial treatment.

BLOOD COMPONENT THERAPY

Blood components are the vital part of oncological supportive care. The primary disease as well as chemotherapy and radiotherapy may suppress hematopoiesis which may require blood component support during treatment. In the hematopoietic stem cell transplant setting, blood components are a necessary part of therapy till engraftment occurs. Excessive use of blood products should be avoided as every transfusion puts the child at an increased risk of transfusion transmitted infections. Blood components are a precious resource and judiciously used will yield the best outcomes.

Packed Cell Transfusions

Bone marrow infiltrative disease like leukemias, lymphomas and at times metastatic solid tumors may cause severe anemia

at presentation. Anemia can also be precipitated by subclinical bleeding due to low platelet counts. Frequent blood tests, infections, hemolysis, underlying iron deficiency, impaired utilization of body iron and low erythropoietin levels all contribute to anemia, which then mimics the anemia of chronic disease. Chemotherapeutic agents which cause bone marrow suppression may also cause symptomatic anemia, adding to treatment morbidity. There is no clear definition as to what constitutes anemia in the pediatric oncology situation. Packed cell transfusions are given at 10–15 mL/kg over 3–4 hours, rounded off to the nearest red blood cell (RBC) unit and used with the following guidelines:

- Anemia with hemoglobin (Hb) of less than 7 g/dL;
- In older children especially adolescents as well as infants, low Hb is less well tolerated and a higher threshold of 8 g/dL may be needed for transfusion especially if symptoms of anemia like headache and fatigue occur;
- In children with hyperleukocytosis at diagnosis, packed cell support may have to be delayed, till chemotherapy decreases the white cell count if the child is hemodynamically stable;
- The general condition of the patient, coexisting cardiac or pulmonary compromise, severity of bleeding, stage of treatment, intensity of chemotherapy and planned surgical interventions in the near future all are to be considered when planning a packed cell transfusion. In the earlier settings, Hb of more than 7–8 g/dL may also be an indication for packed cell transfusions;
- In a child with severe thrombocytopenia, at risk of or with a history of a severe bleeding episode in the past is often given transfusions to maintain Hb around a safe level of 8–10 g/dL.

Platelet Transfusions

Factors causing thrombocytopenia are similar to those causing anemia. Both the disease and the chemotherapy not only cause platelet numbers to decrease but also affect platelet function. Platelet transfusions are used both for bleeding due to thrombocytopenia and are also given prophylactically, which may prevent serious bleeds in a child on chemotherapy. Most platelet transfusion guidelines are based on adult studies of patients with AML and have been extrapolated to children. The general guidelines for platelet transfusions are:

- Any bleeding child with platelet counts $< 50 \times 10^9$/L,
- Prophylactic transfusion for platelet counts $< 20 \times 10^9$/L especially during therapy for leukemia and non-Hodgkin lymphoma (NHL),
- Certain factors may increase the severity of thrombocytopenia and hence the risk of bleeding. Fever, sepsis/DIC and splenomegaly worsen thrombocytopenia and the presence of these may decrease the threshold for prophylactic platelet transfusions,
- Procedures like lumbar puncture for intrathecal therapy, placement of central venous lines or chemotherapy ports require a platelet count of more than 50×10^9/L,
- Patients with AML, especially APML (AML M3) are known to have DIC contributing to severe thrombocytopenia and require aggressive platelet support during induction therapy with a threshold of $30–50 \times 10^9$/L,
- More recent data has shown that platelet counts of more than 10×10^9/L may not warrant prophylactic platelet transfusions as long as there are no other factors contributing to bleeding like fever or coagulopathy.

The general dose for platelet transfusions is 1 unit of random donor platelets per 10 kg. This will increase the platelet counts by $30–50 \times 10^9$/L. Four platelet units per m² of body surface area (BSA) is another method of dose calculation. Various factors affect the rise

in platelet counts after an infusion of platelets. Common extrinsic factors include the ABO compatibility of the unit, platelet specific antigens, duration of storage of platelets and collection methods. Common patient related factors affecting post-transfusion platelet increment include consumptive states like active bleeding, sepsis, fever, splenomegaly and DIC. Alloimmunization because of repeated platelet transfusions and medications may also affect the increase in platelet counts. Platelet transfusions are given over 30–60 min. During the infusion, the patient needs to be monitored for allergy or anaphylaxis. Fever during or immediately after transfusions can occur due to infections from bacterial contamination of platelets.

Special modifications of blood products for use in the pediatric hematology-oncology settings include:

Leukoreduction
This is a method of reducing the white blood cells (WBCs) in every transfused unit of packed cells or platelets. The reduction in white cells is desirable as WBCs increase the chances of transmission of viral (e.g., Cytomegalovirus [CMV]), bacterial and protozoal infections. The transmission of CMV is particularly important in the oncology and stem cell transplant set-up as this CMV can cause disseminated disease in the immunocompromised host. The WBCs also contribute to the antigenic load leading to alloimmuization and febrile nonhemolytic reactions. Hence, WBC removal is essential in some situations (e.g., post-transplant) and can be achieved by various methods like filtration and washing of blood products. The filtration can be done either in the blood bank before storage of blood components or at the bedside with filters attached to the component unit.

Irradiation
This is recommended to prevent transfusion associated graft versus host disease (TA-GVHD). This serious, often fatal immunological complication occurs when transfused cells have active T lymphocytes which attempt to engraft in the immunocompromised host. The symptoms are similar to the poststem cell transplant GVHD and consist of a combination of fever, vomiting, diarrhea and skin rash. Hepatic dysfunction and pancytopenia may also occur. This can be prevented by irradiating all packed cell and platelet units at a dose of 2,500 cGy which inactivated the T lymphocytes by damaging the DNA.

HEMATOPOIETIC COLONY STIMULATING FACTORS

These factors may be directed towards the red cell, or the granulocytic series. The most commonly used cytokine in pediatric oncology is granulocyte colony stimulating factor (GCSF). When intensive chemotherapy is given it results in prolonged periods of neutropenia putting the child at risk for infections. Decreasing the duration of neutropenia aims to decrease the risk of infections and give the intense chemotherapy as per the schedule with no delays due to low counts or infections. Herein, colony stimulating factors can be used in the following four settings: (1) Primary prophylaxis: Following intense chemotherapy even before neutropenia in an attempt to decrease duration of neutropenia and hence prevent infections. (2) Secondary prophylaxis: Prevent development of febrile neutropenia if a previous chemotherapy cycle has resulted in infection and hence a delay in subsequent chemotherapy. (3) Administration after neutropenia has occurred. (4) Administration during febrile neutropenia.

Primary prophylaxis has been found to decrease the incidence of febrile neutropenia, length of hospitalization and in the use of amphotericin. There is currently lack of data to support its use as secondary prophylaxis in children. For children with febrile neutropenia, some subgroups are at increased risk of complications. These include proven pseudomonal or fungal infections, severe sepsis, pneumonia, multiorgan dysfunction, prolonged neutropenia (for more than 28 days) or in infants. Studies have shown that GCSF use decreases duration of antibiotic use, hospital stay and hence cost of therapy of febrile neutropenia. Most literature has used 3–5 µg/kg/day and higher doses have not been found to affect overall results. GCSF is usually started between 1 day and 5 days after completion of the course of chemotherapy and is conventionally continued till the ANC increases to over 1,500/mm^3. While both intravenous and subcutaneous routes have been used, the subcutaneous route has been found to be more efficacious.

NUTRITION

Assessment of malnutrition both at time of diagnosis and at regular intervals during treatment is essential. Better nutrition during therapy will lead to better outcomes as children will tolerate chemotherapy better and recover faster from infectious complications. Children with advanced stages of solid tumors and acute myeloid leukemia are more prone to malnutrition. A decreased intake and the hypermetabolic state in these children both contribute to malnutrition. The following common guidelines help children improve and optimize intake during treatment:
- Frequent small meals which are calorie dense,
- Judicious and liberal use of antiemetics during therapy,
- Avoidance of force feeding during chemotherapy as this causes food aversion even when not on treatment,
- Ensuring adequate intake of fluids,
- Use of bland foods and soft preparations for children with painful mouth ulcers and mucositis,
- Feeding with nasogastric tubes in maintaining the daily caloric requirement in children not willing to take adequately orally,
- Parenteral nutrition is the preferred route in children who need prolonged gut rest due to severe gastrointestinal (GI) mucositis or neutropenic enterocolitis.

PAIN MANAGEMENT

Children with cancer suffer pain due to various factors: (1) procedural pain, e.g., bone marrow or lumbar puncture (2) bone and marrow infiltration pain (3) pain of mucositis (4) neuropathic pain. Every pediatric oncology unit should have protocols in place to address the various types of pain at diagnosis and treatment. Procedures should be done with adequate intravenous sedation (with agents like ketamine and propofol) and local anesthesia. Most bone infiltration pains decreases with the initiation of chemotherapy. Radiation therapy may be needed to give palliative relief to the bone pains of metastatic cancers. Consultation with pain specialists is extremely useful and a graded approach to NSAIDs and opioids is helpful **(Table 11)**. Pain and palliative care specialists also play a key role in relapsed and refractory cases.

NAUSEA AND VOMITING

Nausea and vomiting are among the most common side effects of chemotherapy which compromise the quality of life of children with cancer and hence should be managed aggressively. **Tables 12 and 13** list the emetogenic potential of common chemotherapy agents and their management options.

Table 11 World Health Organization (WHO) pain management ladder

• Provides an easy tool for assessment and therapy of pain
• Prompt administration and given *by the clock* rather than *as required*
• Nonopioids, weak opioids and strong opioids are the mainstay
• Right drug, right dose and right time is emphasized

• Step 1
  – Paracetamol
  – NSAIDs

• Step 2
  – Tramadol
  – Codeine
  – Buprenorphine

• Step 3
  – Morphine
  – Oxycodone
  – Fentanyl

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 12 Emetogenic potential of chemotherapy agents

• High risk:
  – Cisplatin
  – Dacarbazine
  – Actinomycin D
  – Cyclophosphamide

• Moderate risk:
  – Dauno/doxorubicin
  – Cytarabine
  – Carboplatin
  – Ifosfamide

• Low risk:
  – Vincristine
  – Vinblastine
  – Etoposide

Table 13 Therapy for emesis

Risk assessment	Options of therapy
High/moderate	Ondansetron *PO*: 4–11 years old = 4 mg PO scheduled q8h ≥ 12 years old = 8 mg PO scheduled q8h *IV*: 0.15 mg/kg/dose (maximum 8 mg/dose) scheduled q8h ± Dexamethasone 5 mg/m²/dose given once daily prior to chemotherapy (maximum 10 mg/dose)
Low	Ondansetron
Delayed emesis	Dexamethasone Aprepitant or Fosaprepitant
Breakthrough vomiting	Lorazepam *IV*: 0.05 mg/kg/dose q6h PRN (maximum 2 mg/dose) Metoclopramide *IV*: 0.1–0.2 mg/kg/dose q6h (maximum 10 mg/dose) Promethazine *PO*: 0.25–1 mg/kg/dose q6h (maximum 25 mg/dose)

IMMUNIZATION

As many young children receive chemotherapy, a common concern is regarding their vaccination. Due to their immunosuppressed state, issues of whether an adequate immune response will be mounted and whether live attenuated vaccines can themselves cause the disease they are meant to prevent need to be addressed. As a rule, all live vaccines are contraindicated during chemotherapy. As the efficacy of killed vaccines in the immunosuppressed host is questionable, they are also not routinely given. A gap of 3–6 months after completion of chemotherapy and a gap of 12 months after undergoing stem cell transplantation respectively is preferred before restarting vaccination. While the oral polio vaccine is contraindicated in the patient and in the house hold contacts of the child, other live vaccines like varicella can safely be given to household contacts. Children, after completion of aggressive chemotherapy for certain cancers and stem cell transplantation, lose their protective immunity and require reimmunization 6–12 months after therapy cessation.

IN A NUTSHELL

1. Febrile neutropenia is the most common and important oncological emergency.
2. Urgent antimicrobial use and careful monitoring ensures excellent recovery from febrile neutropenia.
3. Risk stratification and biochemical monitoring helps in the diagnosis of biochemical tumor lysis syndrome and prevents progression to clinical tumor lysis syndrome.
4. Spinal cord compression requires urgent multidisciplinary evaluation and therapy.
5. Optimal use of blood components helps in improved outcome. Colony stimulating factors help in faster recovery from neutropenia.
6. Pain and palliative care issues need the attention of specialists and should be adequately addressed.
7. Attention to nutrition during treatment contributes to better cure rates.

MORE ON THIS TOPIC

Bercovitz RS, Josephson CD. Thrombocytopenia and bleeding in pediatric oncology patients. Hematology Am Soc Hematol Educ Program. 2012;2012:499-505.

Fisher MJ, Rheingold SR. Oncological emergencies. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2011. pp. 1125-51.

Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56-93.

Koh AY, Pizzo PA. Infectious complications in pediatric cancer patients. In: Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2011. pp. 1190-242.

Oberoi S, Suthar R, Bansal D, Marwaha RK. Febrile neutropenia: outline of management. Indian J Pediatr. 2013;80:138-43.

Mughal TI, Ejaz A, Foringer JR, Coiffier B. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. Cancer Treat Rev. 2010;36:164-76.

Chapter 45.16
Hematopoietic Stem Cell Transplant

Satyendra Katewa, Satya Prakash Yadav

The field of Bone marrow transplant (BMT) now called as hematopoietic precursor cell transplant (HPCT) holds a history of more than 50 years. The first ever BMT was done in 1956 by E Donnall Thomas in New York for a kid with acute leukemia (donor was an identical twin), which later in 1990 resulted in a Nobel Prize for him. This was the time when very little was known about the graft (donor cells or organs) tolerance, and exercising a cell or an organ transplant was a farfetched idea. As many of the contemporary physicians considered Dr Thomas's treatment approach very risky, it took more than 10 years for the first ever human leukocyte antigen (HLA) matched sibling BMT to happen in a kid with severe combined immunodeficiency disease (SCID) at university of Minnesota. This was performed in 1968 by Dr Robert A Good, who is known as the founder of modern immunology. Following this, rapid development of science related to HLA matching and graft tolerance facilitated the first ever matched unrelated donor (MUD) BMT in year 1973 and since then it is one of the most rapidly developing field in the history of medical science. BMT in children is a vast subject and to discuss

this in detail is beyond the scope of this chapter. We provide here basic but comprehensive understanding of BMT, by discussing the salient aspects of pediatric BMT in this chapter.

TYPES OF BONE MARROW TRANSPLANT

Bone marrow transplant is basically transfusion of healthy hematopoietic precursor cells in an attempt to repopulate a damaged or diseased marrow. When bone marrow (hematopoietic stem cells, mesenchymal stem cells and the whole microenvironment) is used as a source of stem cells, then it is called a BMT and when we use hematopoietic precursor cells only (after peripheral stem cell harvest) the transplant is known as HPCT. In either type of transplants, the most important cell to repopulate a marrow is hematopoietic stem cell and that's why the umbrella term for these transplants is known as hematopoietic stem cell transplants (HSCT). These cells can be patient's own (autologous HSCT) or from an appropriately selected healthy donor (allogeneic HSCT). The basic framework/steps of a hematopoietic stem cell transplant are shown in **Figure 1**. The indications and status of HSCT in these conditions is described in **Table 1**.

Autologous Hematopoietic Stem Cell Transplants
In autologous HSCT, the basic principal used is the steep dose-response curve shown by many chemotherapeutic drugs in the treatment of pediatric solid tumors. This steep dose-response curve between chemotherapeutic agent dose and cancer cell kill

Day-0 is day of transplant
In auto-HSCT: Infuse previously stored stem cells of the patient
Allogenic HSCT:
• *BMT:* Admit the donor, harvest bone marrow ↓ GA and infuse to patient via an IV line
• *Peripheral blood stem cell transplant:* Donor is given G-CSF for 5 days prior to day-0 and then stem cells are harvested in blood bank via a central line and infused immediately to the patient

Conditioning (day-10 to day-0)
(Chemo ± radiation ± serotherapy)
• Done to make space for donor stem cells and to kill the diseased marrow
• Makes WBC go down by stopping production in bone marrow
• Have common toxicities of conditioning like nausea, vomiting, mucositis, renal failure, cardiac failure, infections, etc.

Supportive care (day-10 till engraftment)
• To fight out infection→use of antibiotics and antifungals
• Blood products to keep blood parameters in range
• Care for possible complications like veno-occlusive

Engraftment (mostly around day +15 but in cord blood transplant around day +30)
Definition: Day one of the three consecutive days where absolute neutrophil counts are > 500/mm^3
To be careful about engraftment syndrome

GvHD: Likely to come as early as engraftment happens. As a rule diagnose and treat GvHD as early as possible. If starts before day +100 → acute GvHD, after day +100 → chronic GvHD
Aggressive viral surveillance is also suggested for pre-emptive treatment

WBC

WBC

Day -10   Day -0   Day +15   Day +30   Day +100   Day +365

Prophylaxis for GvHD starts from day-3 till 9–12 months post-HSCT
Commonly used drugs are cyclosporine or tacrolimus or mycophenolate mofetil and or 3–4 dose of methotrexate

Figure 1 Basic framework of allogeneic HSCT
Abbreviations: HSCT, hematopoietic stem cell transplants; GvHD, graft versus host disease; WBC, white blood cells; BMT, bone marrow transplantation; G-CSF, granulocyte-colony stimulating factor.

Table 1 Common indications and transplant recommendations

Disease	Risk group	Autologous HSCT	Allogeneic HSCT		
			Matched sibling	Matched unrelated donor	Haploidentical HSCT
Transplant in malignant diseases					
Acute lymphoblastic leukemia	Very high-risk leukemia at diagnosis High-risk leukemia postrelapse Persistent minimal residual disease Induction failure All other leukemia with 2nd relapse	Proven not to be effective through well-designed trials	R Survival ~60–65%	R Survival ~60%	Exp—Only in refractory leukemia where no other donor option available Survival ~ 50%
Acute myeloid leukemia	High and intermediate-risk AML Persistent minimal residual disease Induction failure All relapsed AML	Proven to be as effective as chemotherapy so not recommended	R Survival ~60%	R Survival ~60%	Exp—Done in conditions where matched related or unrelated donors are not available Survival ~60%
Chronic myeloid leukemia	CML with T315I mutation CML with intolerance to 1st line tyrosine kinase inhibitor (TKI) Poor response to 1st or 2nd line TKI	NR	R Survival ~85%	R Survival ~75–80%	Exp—Done in conditions where matched related or unrelated donors are not available Survival ~70–75%
Myelodysplastic syndromes	Intermediate and high-risk MDS Therapy related MDS	NR	R Survival ~60%	R Survival ~60%	Exp—When no other options available Survival ~45 to 50%
Neuroblastoma	High-risk and relapsed neuroblastoma	R (RCT supports it) MIBG therapy with stem cell rescue (Not supported with RCT) Survival in HR ~65 to 70%	Exp (NK mismatch transplants)	Exp (NK mismatch transplants)	Exp (NK mismatch transplants)
Medulloblastoma	High-risk	Established Survival in average risk ~90% Survival in poor risk ~ 75%	NR	NR	NR
Hodgkin lymphoma	Recurrent and refractory Hodgkin lymphoma	R Survival ~70%	Exp—Being done in postautologous HSCT relapsed cases but efficacy not proven through RCT	Exp—Done in post-autologous HSCT relapsed cases but efficacy not proven through RCT	Exp—Done in post-autologous HSCT relapsed cases but efficacy not proven through RCT
Non-Hodgkin lymphoma	Refractory or recurrent NHL	R Survival~ 65%	Being done but not superior to auto-HSCT except lymphoblastic lymphoma	Being done but not superior to auto-HSCT except lymphoblastic lymphoma	Exp
Ewing sarcoma	Metastatic Ewing and relapsed metastatic Ewing	Done as few small trials favor it but efficacy not proven in RCT	NR	NR	NR
Rhabdomyosarcoma	Recurrent or refractory rhabdomyosarcoma	Done as few small studies favor it but efficacy not proven in RCT	NR	NR	NR
Wilms tumor	Recurrent and refractory Wilms	Established efficacy in phase II trials but RCT not done yet	NR	NR	NR

(Contd...)

(Contd...)

Transplants in benign hematological disorders and immunodeficiency					
Thalassemia major	Pesaro class I, II and III	NR	R Survival ~80–85%	R Survival ~80%	Exp
Sickle cell anemia	Patients with stroke, >3 acute chest syndrome/year, red cell alloimmunization, nephropathy, avascular necrosis of bones, repeated veno-occlusive crises and abnormal Doppler flows in cranium	NR	R Survival ~90%	R Survival ~80–85%	Exp
Bone marrow failure syndromes	Fanconi anemia Shwachman-diamond syndrome Diamond blackfan anemia Dyskeratosis congenital	NR	R Survival ~ 85%	R Survival ~80%	Exp
Aplastic anemia	All young individuals with diagnosis	NR	R Survival ~85–90%	R Survival ~80%	Exp
Severe combined immunodeficiency (SCID)	All SCID types	NR	R Survival ~80%	R Survival ~80%	Exp
Wiskott-Aldrich syndrome	All patients	NR	R	R	Exp
Hyper IgM syndrome	All patients	NR	R	R	Exp
Familial HLH	Patients with perforin, MUNC, etc., mutations	NR	R Survival ~80–85%	R Survival ~80–85%	Exp
Chediac-Higashi syndrome Griscelli syndrome X-Linked lymphoproliferative disease (XLP)	All patients	NR	R Survival ~80%	R Survival ~ 80%	Exp
Severe congenital neutropenia Leukocyte adhesion disorder Chronic granulomatous disease	All patients	NR	R	R	Exp
Transplants in autoimmune and metabolic diseases					
Juvenile systemic sclerosis Juvenile SLE JIA Crohns disease Vasculitis Polymyositis-dermatomyositis Type I diabetes	Refractory to steroids and other immunosuppressive drugs	Being done with evidence from few well designed trials	Exp	NR	NR
Refractory cytopenia	Refractory to steroids and other immuno-suppressive drugs	R	R	R	NR
Aspartylglucosaminuria Wolman disease Late infantile metachromatic leukodystrophy Niemann-Pick C(2)	All patients	NR	R	Exp	Exp
Osteopetrosis	All patients	NR	R	R	Exp
Epidermolysis bullosa Dystrophicans	All patients	NR	R	R	Exp

Abbreviations: R, recommended; NR, not recommended; Exp, experimental; HSCT, hematopoietic stem cell transplants; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; MDS, myelodysplastic syndromes; RCT, randomized controlled trials; MIBG, metaiodobenzylguanidine; HLH, hemophagocytic lymphohistiocytosis; SLE, systemic lupus erythematosus; JIA, juvenile idiopathic arthritis.

connotes that if the drug dose is increased without increasing toxicity to the patient, then a multiple log increase in tumor cell death would be observed. Autologous HSCT allows the increase in the chemotherapy doses above those limited by myeloablation and this increases the tumor kill. The chemotherapeutic regimens (conditioning) used in autologous HSCTs are therefore combinations of chemo agents that have shown antitumor activity but of course we use them at a higher dose in an attempt to maximize antitumor cytotoxicity. Since, the doses of chemo-radiation in these transplants are likely to ablate the marrow so these patients undergo stem cell collection prior to the transplant. For this, patient is given marrow growth factors (G-CSF: granulocyte colony stimulating factors) after chemotherapy which mobilizes the stem cells from bone marrow to peripheral blood and then these mobilized stem cells are harvested through a peripheral access (dialysis catheter) and this whole process is called peripheral stem cell harvesting. In an autologous HSCT, post high-dose chemotherapy, since we rescue the marrow with healthy stem cells, these HSCTs are now known as high dose chemotherapy with stem cell rescue.

High-dose chemotherapy with stem cell rescue is a potentially curative option for children with chemotherapy sensitive high-risk solid tumors which are not curable with conventional multimodality therapy, provided if done in the setting of minimal disease. Although, out of all the solid tumors, neuroblastoma is the only tumor that have shown better survival rates with autologous HSCT compared with standard chemotherapy in a randomized controlled trial, this treatment is frequently used to treat other high-risk solid tumors such as brain tumors, non-Hodgkin and Hodgkin's lymphoma, Ewing sarcoma, rhabdomyosarcoma, Wilm's tumor, osteosarcoma and retinoblastoma.

One has to be careful about the complications associated with these transplants including infection related, veno-occlusive disease of the liver and lung, idiopathic pneumonia syndromes and organ toxicities particularly renal and auditory toxicities. These complications add a potential risk of mortality and long-term morbidities in these patients and thereby have to be discussed at length with patients and their families while offering the autologous HSCT option particularly in the resource poor settings where the outcome can be disastrous.

It can be concluded that in children and adolescents with high-risk solid tumors, autologous HSCT along with multiagent chemotherapy, radiation and surgery has demonstrated promising results but disease recurrence remains a challenge. Research is required to define specific patients' subgroups where either autologous HSCT would be of help or not at all. The emerging post-transplant immunomodulatory therapies such as vaccines (against tumor antigens), cytokines or antibodies (against tumor antigens) needs to be evaluated in much larger studies and focus has to be on newer possibilities such as incremental role for allogeneic HSCT post-autologous HSCT to provide cure by graft versus tumor effect. Further research is needed to improve the results in many poor prognosis tumors.

Allogeneic Hematopoietic Stem Cell Transplants

Allogeneic HSCT are very different from the autologous HSCT. Unlike autologous HSCT, the stem cells used are from nonself, known as donor derived. The prerequisite to be an optimal donor for an allogeneic transplant is good matching of HLA between the donor and the patient. If patients HLA is matched with one of the family member (sibling has 25% chance to be matched, and chances of other family members getting matched is < 5%), it is called a matched related donor transplant but if HLA matches with someone outside the family, it is called MUD transplant. If the donor is from the family but not completely matched then this transplant is known as mismatched related donor transplants

and similarly for unrelated donors, it is labeled as mismatched unrelated donor transplants. In a nutshell, when we consider an allogeneic HSCT, the first thing to be done is a detailed HLA matching between patient and the potential donors. **Table 2** details the common complications and their management in stem cell transplantation and **Figure 2** shows the time line of infectious complications. In the next paragraph we describe the basics and importance of HLA matching in allogeneic transplants.

THE SCIENCE OF HLA AND MAJOR HISTOCOMPATIBILITY COMPLEX

Major histocompatibility complex (MHC) is a chromosomal region with genes which code for individual-specific tissue antigens. In humans, the MHC region is located on the short arm of chromosome 6 (6p) and is designated as HLA region. HLA is a relatively large area on chromosome 6. In a HLA region, most (but not all) of the genes regulates the immune responses in an individual. The HLA region has been divided into class I, class II, and class III regions, each containing numerous gene loci that encode a large number of polymorphic alleles. Antigens from class III are not thought to play a significant role in transplantation and therefore are not used to identify donor/recipient matching in the current practice. Each antigen is composed of two alleles. The class I HLA antigens include HLA-A, B, and C antigens and are present on almost all cells of the body at a varying expression. There have been other class I antigens as well but are not considered important due to their restricted expressions on the cell. The class II antigens are further divided into DR, DQ, and DP antigens. Class II antigens are expressed on B-cells and monocytes and can be induced on many other cell types following inflammation or injury.

In a normal individual, when the immune system develops, the cells of immune system are exposed to the self-antigens in a process called tolerance (central and peripheral) and only the tolerant immune cells are allowed to survive and form a functional but healthy immune system. Whenever there is a break in the tolerance system, the outcome is an autoimmune disease. In an allogeneic HSCT, hematopoietic stem cells from a donor establish a new immune system in the patient. The cells of this new immune system have not been exposed to the antigens of the patient and they are obviously not tolerant to these antigens. The intensity of cross-talk between the cells of this new immune system and the patients' antigen (tissue) depends upon the matching of the HLA expression between the patient and the donor. The reaction of these new immune cells towards patients' antigen is known as graft versus host disease (GvHD), the most dreaded complication of transplant. In other words severity of the GvHD depends on how imperfectly a patient and donor are matched (lesser the matching more severe is the GvHD).

In an individual, 50% of HLA is inherited from each parent and as per the Mendelian law of inheritance, there is only 25% chance that the next sibling will inherit the same HLA from same parents. In other words, when we start looking for a HLA matched sibling in a family, in the present scenario (average family with two children) the chances to find a matched sibling is just 25%, which increases considerably with increase in the numbers of siblings.

Human leukocyte antigen typing is done by both serology and DNA based technique. It is of two types: (1) low resolution; and (2) high resolution. Low resolution primarily means testing the antigens (not alleles). The low resolution typing can be done by serology and molecular techniques both. The high resolution typing is done by DNA based techniques and this includes typing at antigen as well as their alleles. **Table 3** details how to read a low and high resolution HLA typing report. High resolution typing is a prerequisite in an unrelated HSCT (MUD and cord blood unit

Table 2 Major complications in hematopoietic stem cell transplants

Type of complications	Possible interventions
Chemotherapy-related toxicity • *General*: Mucositis, nausea, vomiting and diarrhea • *Liver*: Veno-occlusive disease (VOD) and transaminitis • *Lungs*: Pulmonary fibrosis. Idiopathic pneumonia syndrome (IPS) particularly in allogeneic HSCT • *CNS*: Seizures, white matter changes and posterior reversible encephalopathy syndrome (PRES)	• Antiemetics for nausea and vomiting • Fluids and electrolytes replacement for diarrhea • *Liver*: Defibrotide for veno-occlusive disease both as prophylaxis and treatment for high-risk candidates and for treatment of VOD as well. It is particularly a problem in transplants of neuroblastoma (autotransplants), thalassemia and leukemia (allogeneic transplants) • *Lungs*: To avoid combining multiple pulmonary toxic agents if possible. For example, Busulfan and total body irradiation • IPS has high mortality and an early and aggressive immunosuppression is helpful • *CNS*: To continue prophylactic antiseizure drugs during maximum risk time of drug induced seizures and strict control of blood pressure for PRES
Infectious complications • Bacterial sepsis, mostly gram-negative and gram-positive usually central venous line related • Reactivation of viral infections particularly cytomegalovirus, EB virus and varicella • Fungal infections particularly *Candida* and *Aspergillus*	• To start broad spectrum antibiotics as early as possible (selection of antibiotics depends on the local flora in the unit • To keep an aggressive surveillance for viral reactivations (frequent viral PCRs) and to start early treatment (pre-emptive treatment) • To start antifungal prophylaxis from day of transplant as then to continue till optimal immune reconstitution is achieved Viral and fungal problems are particularly a problem in allogeneic transplants as immune reconstitution is much delayed in allogeneic than in autologous HSCT
Graft versus host disease (GvHD) • Acute GvHD (Onset < 100 days) • Chronic GvHD (Onset > 100 days)	• GvHD is the most dreaded complication post-HSCT. As a general rule, more the HLA mismatch is, more is the GvHD. Acute GvHD involves skin, gut and liver and chronic GvHD can involve almost any organ system of the body • In matched sibling and MUD HSCT, GvHD is less with BMT than a peripheral blood stem cell transplant. Cord blood unit transplant also carries a less risk of GvHD then a PBSC or BM transplant. It is very less with T-cell depleted HSCTs • The primary or first-line of therapy for the treatment of a GvHD is combination of systemic corticosteroids with a calcineurin inhibitor (cyclosporine or tacrolimus) • Other treatment options are mycophenolate mofetil, rapamycin, cyclophosphamide, extracorporeal photopheresis (ECP), antithymocyte globulin (ATG), infliximab, etanercept, rituximab, mesenchymal stem cells, etc. • This is the most important hurdle in succeeding through the barriers of HLA mismatching

Late effects
• These effects primarily depends on the conditioning regimen used
  – Total body irradiation (TBI) in conditioning makes patients prone for late endocrinal problems particularly hypothyroidism, adrenal insufficiency or growth hormone insufficiency and cataract
  – TBI-based regimens also adversely affects the growing brain (age < 5 years) particularly the calculative math skills
  – A combination of TBI with alkylating agent increases the chances of late onset cardiotoxicity more so if anthracyclines have been used in past
  – In patients where TBI in used in conditioning and patients developed GvHD, the chances of bronchiolitis obliterance syndrome (BOS) are higher
  – An alkylating agent (cyclophosphamide, busulfan, treosulfan, etc.) in the conditioning regimen makes the likelihood of infertility around 35–85%
	• The most important risk factors for long-term side-effects post-HSCT are age at transplant, gender, associated comorbidities, conditioning used, presence of GvHD post-transplant and primary disease
	• TBI-based conditioning have been associated with high incidence of endocrinal deficiencies, growth impairments and poor bone health
	• The risk factors for poor bone heath are gender, age, physical inactivity, poor nutritional status, inadequate intake of calcium and/or vitamin D, Caucasian or Asian race), chemotherapy, TBI/craniospinal irradiation, corticosteroids, cyclosporine, granulocyte-colony stimulating factor, endocrine deficiencies, GvHD and/or its treatment, direct effects of conditioning regimens on bone marrow stromal cells
	
	• Anthracyclines and cyclophosphamide are the most common culprit in causing cardiotoxicity. The other less frequently known and less harmful agents are 5-fluorouracil, mitoxantrone, carmustine, amsacrine and interferon
	
	• The most commonly found risk factors for BOS are TBI-based conditioning, peripheral blood stem cell transplants and presence of GvHD. Out of all these GvHD is the strongest risk factor predicting BOS post-transplant
	
	• Alkylating agents and TBI-based regimens have been associated with infertility both in males and females with variable rates. There have been pregnancy reported with use of single agent cyclophosphamide use but the scenario is worst when it is in combination with busulfan and TBI

transplants), as the impact of antigen and allele mismatch equally but adversely affects the transplant outcome. In matched related sibling transplants, as the donor also has received HLA haplotypes from the same parents, it is very likely that antigen matching means matching at the allele level as well. This is the reason for doing only low resolution typing in matched sibling HSCTs.

The importance of matching at HLA class I and II is well established. In a large retrospective study, it was shown that HLA matching all class I and II antigen and alleles is associated with lower GvHD, early immune reconstitution and overall better survival. It is very important to note that a 100% matched (HLA-A, -B, -C, -DR, -DQ) donor does not mean a match at minor antigens (which we have not tested) level. It is thought that the mismatch at minor antigen level incites GvHD even in 100% matched sibling transplants. These mismatches, since are at minor antigen levels with limited antigenic expression, poses a smaller challenge as

	D-0	D 15–45	D-100	D-365
	(Engraftment in bone marrow or PBC transplant 12–18 days) (Engraftment in cord blood transplant happens up to 42 days) (Engraftment syndrome—an important d/d of infection at this time)			

Phase	Pre-engraftment – Neutropenia – Mucositis – Central venous catheter	Postengraftment – Impaired cellular and humoral immunity – NK cell recovery, CDS+increasing but T-cell repertoire restricted	Late effects – Impaired cellular and humoral immunity – B-cell and CD4+ T-cell number recovers slowly	
GvHD		Acute GvHD	Chronic GvHD	
Bacterial	Gram-negative bacilli Gram-positive organisms Gastrointestinal streptococcal infection		Encapsulated bacteria	
Viral	Herpes simplex virus CMV RSV and enteric viruses HHV	EBV PILD	VZV	
Fungal	Aspergillus Candida	Pneumocystis		

Figure 2 Time line of infections during the course of HSCT

Abbreviations: D, day; GvHD, graft versus host disease; CMV, cytomegalovirus; RSV, respiratory syncytial virus; VZV, varicella zoster virus; HHV, human herpes virus; EBV PTLD, Ebstein-Barr virus post-transplant lymphoproliferative disease; Bars, thicker the bar commoner the infection, thinner the bar vice versa.

Table 3 Basic reading of a HLA report

Example	Technique	Level of resolution
HLA-A2	Serological	Low
HLA-A*02	Molecular	Low
HLA-A*020101	Molecular	High resolution of one antigen
HLA-A*020101 HLA-A*240301	Molecular	High resolution of both the A antigens

The use of * suggest molecular (DNA based) testing
In a high resolution HLA report, the letter before (*) and the first two numbers after (*) constitute an antigen. The last four numbers post (*) are two alleles of an antigen. For example, in HLA-A*020101, A*02 is the antigen and 01, 01 are two alleles of antigen A*02. In the above report of HLA-A*02 and -A*24 are two antigens.

far as GvHD is concerned. The fighting between donor cells and recipient cells has a positive outcome in both malignant and non-malignant indications of HSCT. In nonmalignant conditions, this fight causes eradication of recipient's residual marrow ensuring a stable engraftment and in malignant indications it causes graft versus leukemia (GvL) effect which is the primary cause of tumor kill in allogeneic transplants. In other words, in allogeneic HSCT, clinical GvHD means GvL also but absence of clinical GvHD does not rule out an ongoing GvL. It has been found

that even one antigen or allele mismatch adversely affects the outcome of an allogeneic HSCT, increasing the mismatches at antigen or allele level severely affects the overall survival even in all types of HSCT including a sibling transplant. **Table 3** summarizes major complications in the setting of an allogeneic HSCT.

MATCHED UNRELATED DONOR TRANSPLANT

In matched but unrelated donor transplants (MUD), although patient is matched at all the tested major antigens (HLA-A, -B, -C, -DR, -DQ) but since donor is not related to the patient, there is a good chance of minor antigen mismatch in these situations. This mismatch poses the biggest challenge in MUD transplants, i.e., GvHD. GvHD in these patients is very severe and affects adversely the transplant outcomes. It has been found that mismatch at HLA-DQ antigen or allele is not associated with adverse outcome, suggesting that matching at HLA-A, -B, -C, -DR is a must but mismatch at HLA-DQ may be tolerated. This finding has shifted the gold standard of matching requirement from 10/10 to 8/8 in MUD transplants.

In the western world, donor registries have a very good local representation and thereby good success with these MUD transplants but unfortunately the representation of developing world in these bone marrow registries is minimal and thereby jeopardizes the chances of finding a good match. This challenge

simultaneously presents the opportunity to the developing countries to build their own bone marrow donor registries with large local representation so that the option of MUD transplant can be exercised safely. The other important reason to have local registries is purely financial. Donor stem cell graft from any international registry costs around 15–20,000 USD which is mostly unaffordable in low-income countries. The third important disadvantage of taking a donor from these registries is that the process of obtaining a stem cell graft easily takes 4–5 months and this might adversely affect the outcome particularly if the transplant was planned for a malignant indication (cancer relapses before the transplant) or a bone marrow failure (patient gets colonized with dreaded infections). Hence, MUD transplants are a viable but challenging option in India and should only be done by very experienced centers and transplant physicians.

CORD BLOOD TRANSPLANTS

One other option for an unrelated donor HSCT is umbilical cord blood (UCB) stem cells as source. There are two types of cord blood banks, private banks and public banks. In private banking, cord blood stem cells of an individual are stored at birth for the future use, either for the same individual or for a sibling if found to be HLA matched. The public banks are one where the donated cord units are HLA typed and stored to be used in future for anyone with HLA matching. The developed world, through their public cord banks, is performing UCB transplants very often with good success rates. The HLA matching required for these transplant is slightly different and matching at three antigens or six alleles (HLA-A, -B, -DR) is currently considered gold standard, i.e., a 6/6 match is a perfect match for cord blood transplants. Recently, it has been suggested that matching at HLA-C antigen increases overall survival in cord blood transplants but more research is needed on that. One interesting aspect about UCB transplants is that the less number of stem cells are required for engraftment and current guidelines say that any cord unit having a cell dose [total nucleated cells (TNC)] more than or equal to 2.5×10^7/kg with 6/6 match can be taken as a good donor unit. The TNC dose is one log less than sibling or matched unrelated transplants where TNC dose is usually more than or equal to 5×10^8/kg. Please note that TNC are not stem cell (which are CD34$^+$) but all the nucleated cells in the graft. It is interesting to know that, increasing the TNC dose can compensate for cord unit HLA mismatches. In a 5/6 matched cord blood transplant, a TNC dose of more than or equal to 5×10^7/kg would produce same overall survival rates as a 6/6 matched cord unit with 2.5×10^7/kg would produce. Cord blood transplants induce less GvHD and the exact reason for this is unknown. It is thought to be secondary to the naivety of cord blood stem cells, which post-transplant helps in tissue tolerance. The main problem with cord blood stem cell transplants is delayed engraftment (around 25–35 days) in comparison to matched sibling and MUD transplants (around 15–18 days). This late engraftment in UCB transplants increases the incidence of sepsis and cost of transplants. There is a higher incidence of viral reactivation [particularly cytomegalovirus (CMV)] in these transplants which also adds to the transplant related mortality. **Figure 2** summarizes the timings of different viral reactivations in the setting of an allogeneic HSCT.

MISMATCHED RELATED TRANSPLANTS

In spite of an aggressive MUD and cord blood unit search, around 50% of the eligible patients are still left without a suitable donor and majority of them succumb to their disease in the past especially if it was malignant. Hence, scientists started performing HSCT with 50% matched (haploidentical) donors. The good thing is that every patient has a 50% matched donor available in family as we inherit 50% HLA from each of our parent. To start with, these transplants had very high rate of GvHD (70%) and other complications. Working on this approach, and to decrease the GvHD, the stem cell grafts were filtered out of T cells (cell causing GvHD) and then were infused. These transplants are called as T cell depleted HSCT (TCD HSCT). There were minimal GvHD in these patients but since T cells are very important in fighting against infection and also for engraftment, there was high mortality and morbidity secondary to infections and graft failure in these transplants. The large rejection rates were later overcome by a mega dose ($\geq 10 \times 10^6$/kg CD34$^+$) of stem cells in these HSCT. Since the cost associated with these transplants was very high (separation kit only would cost around 12–15,000 USD$) , these transplants did not become popular with transplant physicians particularly in the developing world.

Since this TCD HSCT had an unusually high incidence of opportunistic infections and transplant related mortality other approaches (haploidentical HSCT with T cells replete graft) were tried and they were found to be encouraging. In early 1960, it was shown that using high dose cyclophosphamide post allogeneic transplant might help in decreasing graft rejection. Luznik et al. at John Hopkins showed that using post-transplant cyclophosphamide in a T-cell replete haplo-HSCT not only decreases the severe GvHD significantly but also decreases infection rates significantly. It was suggested that cyclophosphamide does not damage stem cells, kills the actively proliferating lymphocytes (GvHD causing cells) but preserves the silent lymphocytes (infection fighting cells). This approach is likely to revolutionize the world of HSCT. For patients, who do not have a matched sibling donor available, this approach gives them a dedicated donor in family to avail a HSCT. The most amazing thing about this transplant is that the cost is almost similar to a matched sibling transplant as patient does not have to spend a single penny to get the donor stem cells. We need more research to fine tune these transplants as per patients need so that we have outcomes at par with matched sibling transplants.

Recently a different way of haplo HSCT has been suggested where only the GvHD causing T cells (T cell receptor αβ-TCR αβ) have been depleted from the graft and have produced very encouraging results. Unfortunately, this technique is expensive but does offer an alternative that seems very safe and effective for haploidentical stem cell transplants.

In summary, the field of HSCT has evolved very rapidly particularly in the last decade. Autologous HSCT need to be done further refined so that the chemo-radio intensity of these transplants can be reduced (less toxicity related deaths) without compromising outcome. Matched sibling transplants are already moving towards reduced intensity conditioning with good results and less transplant related mortality. Unrelated transplants, as of today are very costly and risky, and need more research to make them easy to perform and safe to exercise. With the rise of haploidentical transplants, suddenly HSCT world has become very interesting as every eligible patient now has a chance to avail HSCT and that too with good results. More research is needed to make these transplants less costly and toxic so that even small centers can provide these high end transplants to the children in the developing world.

IN A NUTSHELL

1. Pediatric stem cell transplantation is a rapidly advancing field in medicine.
2. The proven indications for an autologous bone marrow transplant are few but are expanding.
3. Allogeneic BMT is curative for many children suffering from benign and malignant hematological diseases.
4. Allogeneic BMT is also practised frequently and successfully for metabolic and primary immunodeficiency diseases.
5. The most initial and important step in an allogeneic BMT is human leukocyte antigen (HLA) matching between the patient and the potential donors (usually siblings).
6. The chance of having one sibling to be 100% HLA match with the patient is 25%.
7. Matched unrelated donor transplants (both cord blood and live unrelated donor transplants) are expensive and effective options but the chances of finding a matched donor from registries depends on the racial representation of the patient in the searched registry.
8. Mismatched related donor transplants (< 100% matched transplants from parents or siblings) are quite promising as every patient has a donor in family who would be at least 50% matched. More research is likely to make these mismatched related transplants safer and more effective.
9. Future stem cell transplants are likely to have reduction in chemotherapy with incorporation of immunotherapy.

MORE ON THIS TOPIC

de la Morena MT, Gatti RA. A history of bone marrow transplantation. Immunol Allergy Clin North Am. 2010;30:1-15.

Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for primary immunodeficiency disease. Bone Marrow Transplantation. 2008;41:119-26.

Guinan EC, Krance RA, Lehmann LE. Stem cell transplantation in pediatric oncology. In: Pizzo PA and Poplack DG. Principles and Practice of Pediatric Oncology. 3rd edition Philadelphia, PA: Lippincott-Raven Publishers; 1997. pp. 800-41.

Klein J, Sato A. The HLA system. First of two parts. New England J Med. 2000;343:702-9.

Kline RM. Pediatric Hematopoietic Stem Cell Transplantation. 1st ed. New York, USA: Informa Healthcare; 2006.

Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. Blood. 2001;98:3456-64.

Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. Cold Spring Harbor Perspectives in Medicine. 2012;2:a011825.

Mehta P, Locatelli F, Stary J, Smith FO. Bone marrow transplantation for inherited bone marrow failure syndromes. Pediatr Clin North Am. 2010;57:147-70.

Toubert A. The EBMT Handbook on Haemopoietic Stem Cell Transplantation. 6th ed. Jane Apperley EC, Eliane Gluckman, Tamas Masszi; EBMT; 2012.

Wynn R. Stem cell transplantation in inherited metabolic disorders. Hematology/ the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2011;2011:285-91.

Chapter 46.1

Approach to A Child with Rheumatological Disorder

Anand Prahalad Rao

Pediatric rheumatology is a nascent subspecialty of pediatrics and is less than a century old. It is also a dustbin specialty wherein all those patients with diseases with multisystem involvement and those with *no diagnosis* are sent in for so called *expert opinion*. But therein, lays the challenge for the pediatric rheumatologist. The traits that are required for the practitioner of this sub-specialty are not very different from other specialties of medicine. The need is for a thorough history, good physical examination and relevant investigations with ultimate sensible assimilation of information that is available. These patients come with long complicated histories and big files containing lot of investigations. Hence, the process is very much like solving a puzzle. Time is the essence and it would be better if these patients are seen in a nonurgent setting.

APPROACH TO A CHILD WITH JOINT PAINS

Joint pain constitutes one of the most common symptom for which a child is referred to a pediatric rheumatology clinic. The first question which needs to be answered is whether this is articular or nonarticular. The following questions in history help differentiate arthritis from nonarthritic causes of limb pain.

Is it Articular/Extra-Articular?

1. Where is the pain? Is it in the joint or outside the joint? In arthritis, pain tends to be localized to the joint whereas, in pain amplification syndromes and growing pains, pain tends to extend beyond the joint.
2. Is there early morning stiffness or gelling? Early morning stiffness refers to pain and difficulty in moving the joints in the morning on waking up and it usually tends to last for about half an hour or more. Gelling is similar to early morning stiffness, but tends to happen after prolonged resting in the daytime. Pain worsening during sleep might indicate the need to look more closely for conditions like malignancy.
3. Is there joint swelling? Joint swelling indicates that it is arthritis.

Is it Inflammatory or Noninflammatory?

The inflammatory conditions are associated with classical signs of inflammation namely warmth, redness, increased temperature and loss of function, i.e., limitation of range of movement. Arthritis is defined as presence of swelling or in absence of swelling, presence of at least two of the above mentioned signs of inflammation. Absence of these signs of inflammation would indicate that it is a noninflammatory condition.

Conditions Associated with Noninflammatory Nonarticular Pain

Growing pains A 5-year-old boy was brought with lower limb pain which happened in the wee hours of the morning. It was relieved with oil massage and oral paracetamol. Next day morning, the child woke up as if nothing happened overnight. This is the classical history of a child with growing pain. It is one of the examples of nonarticular, noninflammatory pain syndromes. A benign condition, it is seen classically in children between the ages of 3–12 years of age, peaking usually between 3 and 5 years of age. The pain is usually bilateral and localized to shin, calves, thighs and popliteal fossa. Decreased pain threshold, vascular changes and stress (overuse of lower limbs) are the various hypotheses that have been put forward to explain this condition. Reassurance and symptomatic treatment with oil massage and paracetamol would suffice and it would be prudent to avoid unnecessary investigations.

Pain amplification syndromes A 10-year-old girl was brought with complaints of pain and swelling of her right lower limb since past 2 months. The swelling was noticed over the whole lower limb with skin being shiny, cold and the whole extremity being very tender to even touch. She had a history of significant sleep disturbance. This is an example of a complex regional pain amplification syndrome. It is more common in preteens and teenagers. There is usually a significant stressor in the social milieu of the patient. The treatment would involve acknowledging to the patient and the care givers the fact that the patient definitely has pain and would involve physiotherapy and behavioral therapy. The disorder can be chronic and only in resistant cases, are drugs like antidepressants used.

Somatization disorder It is classically a disease in which there are many symptoms and not too many signs on examination. These patients come with pain symptoms in anatomically distinct regions with some gastrointestinal and genitourinary symptoms. These symptoms are not feigned and these patients need to be carefully screened for physical/sexual abuse/neglect. A child psychologist is an important person in management of this condition.

Conditions Associated with Periarticular Inflammation

Orthopedic conditions Fractures in periarticular region might rarely simulate arthritis.

Osteomyelitis in the metaphyseal region might give rise to symptoms which can mimic arthritis and sometimes an extension into the joint can cause septic arthritis. There is an entity known as chronic recurrent multifocal osteomyelitis (CRMO) which is auto inflammatory disease of the bone and is seen in the metaphysis of the bone (**Fig. 1**).

Malignancies A 2-year-old boy was brought with complaints of inability to bear weight and walk since past one month. Initially attributed to be due to a trivial fall, the condition progressively worsened. The child used to have night pains and had significant weight loss. Physical examination revealed significant lymphadenopathy and hepatosplenomegaly. The child also had significant bony tenderness. Complete blood count (CBC) revealed
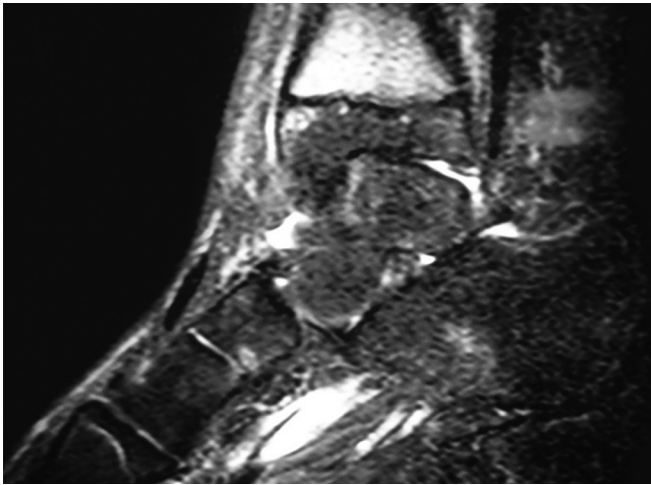
Figure 1 MRI of the ankle showing osteolytic lesion in tibial metaphysis (chronic recurrent multifocal arthritis)

pancytopenia and bone marrow confirmed the diagnosis of acute lymphoblastic leukemia. One of the common differential diagnoses of juvenile idiopathic arthritis (JIA) is malignancy especially acute lymphoblastic leukemia and neuroblastoma. Hence, it is important to take a detailed history and do a good physical examination as the erroneous diagnosis of JIA will lead to immunosuppression and delay the diagnosis of malignancy. The red flag signs for malignancy include weight loss, night pains, constitutional symptoms (fever, night sweats, anorexia), pancytopenia, hepatosplenomegaly, and lymphadenopathy.

Hematological conditions associated with arthritis like manifestations Sickle cell disease is an autosomal recessive condition with recurrent bone pain due to RBC sequestration associated osteonecrosis. Thalassemia can be associated with bone pain and arthritis especially of ankle. Deferiprone, an iron chelating agent has been associated with arthralgia.

ARTICULAR INFLAMMATION/ARTHRITIS

It can be acute or chronic. It is said to be acute if the duration of the disease is less than 3 weeks, subacute if it is between 3 and 6 weeks and chronic if it is more than 6 weeks.

Acute Arthritis

Septic arthritis A 3-year-old boy was brought with history of fever associated with right knee joint swelling and pain for the past 3 days. The knee was so tender that the child refused anybody permission to even come near it. CBC revealed mild anemia and leukocytosis. ESR was elevated. The synovial fluid analysis revealed cell count of $1,00,000/mm^3$ with neutrophilic predominance. Gram stain of synovial fluid showed Gram positive cocci. This is the typical case of septic arthritis. It has to be a differential diagnosis of any acute monoarthritis. Treatment is antibiotics for at least 4–6 weeks.

Reactive arthritis A 10-year-old boy was brought with history of bacillary diarrhea 3 weeks back and had been treated with oral antibiotics. He had recovered completely from the bout when he started having painful swelling of right knee with limitation of movement since past one week. Fever was not very high and CBC showed mild leukocytosis with mildly elevated ESR. This is a typical case of reactive arthritis. It is found to be more common in individuals who are HLA-B27 positive. Treatment is usually with NSAIDs. When reactive arthritis becomes chronic, differentiation from JIA might be difficult.

Rheumatic arthritis A 12-years-old boy was brought with complaints of swelling and pain of both the wrists, knees and ankles since 5 days. It started with knees and subsequently involved the wrists and ankles. On day 5, the knees seemed to get better but wrists and ankles became involved. There was history of sore throat about 2 weeks before. Cardiac examination revealed pansystolic murmur of mitral regurgitation and antistreptolysin-O (ASLO) titers were elevated. This is a text book description of rheumatic fever with arthritis and carditis. Diagnosis would require that revised Jones criteria be followed. Treatment would include treatment of streptococcal pharyngitis with penicillin along with aspirin. Secondary prophylaxis with benzathine penicillin would be required long term.

Poststreptococcal reactive arthritis This is a term used to describe a child who has had a streptococcal pharyngitis following which he develops an arthritis which is protracted, nonmigratory with poor response to aspirin or other NSAIDs. These children do not fulfill the revised Jones criteria. Secondary prophylaxis with benzathine penicillin is recommended for at least one year.

Manifestation of other rheumatological disease Arthritis can be an initial manifestation of systemic lupus erythematosus (SLE), juvenile dermatomyositis, vasculitis and periodic fever syndromes.

Arthritis associated with vaccination Arthritis has been reported with MMR vaccine.

Chronic Arthritis

Infection A chronic infection like tuberculosis of joint can sometimes mimic JIA. The clue would be that it tends to be a monoarthritis in a child with a possible TB contact with strongly positive Mantoux test. Synovial fluid analysis will show increased leukocyte count with lymphocytic predominance.

JIA As it is being covered in detail in subsequent chapters, it would be sufficient to say that this condition affects children less than 16 years with arthritis persisting beyond 6 weeks.

Enthesitis related arthritis It is a form of arthritis which tends to affect older children and adolescents with predominant lower limb arthritis and a tendency to affect the axial skeleton and entheses (sites of insertion of tendons and ligaments onto the bone). There is absence of autoimmune antibodies like ANA and rheumatoid factor and presence of HLA-B27 in majority of these patients. It is called as Juvenile ankylosing spondylitis if there is involvement of sacroiliac joint as confirmed by imaging (X-ray/MRI).

Psoriatic arthritis The presence of arthritis of at least 6 weeks in a child less than 16 years of age with psoriasis or if psoriasis is absent, presence of at least two of the following three criteria: dactylitis; nail pitting; and psoriasis in a first degree relative with absence of following: HLA-B27, rheumatoid factor, features of systemic onset JIA and family history of HLA-B27 associated diseases.

Chronic arthritis can also be associated with other rheumatological disorders including SLE, juvenile dermatomyositis, vasculitis, and periodic fever syndromes.

Conditions Mimicking Chronic Arthritis

There are hereditary conditions which can be mistaken for chronic arthritis and include progressive pseudorheumatoid arthropathy of childhood (PPAC) (**Fig. 2**); epiphyseal dysplasias; Torg Winchester syndrome; CACP syndrome (camptodactyly-arthropathy-coxa vara-pericarditis); and intra-articular arteriovenous malformation, e.g., part of Klippel-Trenaunay malformation (**Fig. 3**). Target joint of coagulation disorders like hemophilia, von Willebrand disease can also present as arthropathy.

Figure 2 X-ray lumbar spine showing platyspondyly which is classical of progressive pseudorheumatoid arthropathy of childhood (PPAC)

Figure 3 MRI of Klippel-Trenaunay syndrome showing arteriovenous malformation of the whole limb. The child presented with recurrent hemarthrosis

APPROACH TO A CHILD WITH MULTISYSTEM DISORDERS

Systemic Lupus Erythematosus

*A 15-year-old boy was brought with complaints of fever for the past 2 months. The fever used to be on and off with history of rash on the face (**Fig. 4**), with oral ulcers. There was history of joint pains in the peripheral joints including the small joints of hands. History of headache was there too. Investigation revealed mild anemia with normal leukocyte count with mild thrombocytopenia. ESR was elevated and urine showed pyuria and hematuria with urine culture turning out to be negative. The urine exam also revealed non nephrotic range proteinuria, ANA by immunofluorescence was positive and anti-dsDNA antibodies were positive too.*

This case vignette shows how a typical case of SLE presents with arthritis. Though the arthritis tends to be nonerosive, it can be crippling. One must think of SLE when one encounters following conditions:

- Febrile illness (DD for FUO)
- Multisystem disease
- Episodic disease
- Inflammatory disease with leucopenia and thrombocytopenia
- Elevated ESR but normal CRP
- Unexplained nephritis/chorea/psychosis/headache.

Juvenile Dermatomyositis

This is a multisystem disease which tends to involve skin and muscle commonly, hence the name dermatomyositis. But, involvement of gastrointestinal tract, lungs, heart and central nervous system is not uncommon. There seem to be distinct subsets of this disease with prognosis varying with the type of involvement. The diagnosis is based on presence of bilateral symmetrical proximal muscle weakness and skin involvement in the form of Gottron papules, heliotrope rash and periungual erythema. The documentation of muscle inflammation in the form of elevated muscle enzymes (CPK, AST, ALT and LDH) and either a muscle biopsy or a noninvasive investigation like MRI of the affected muscles (usually the vastus group of muscles) will be necessary.

Scleroderma

An 11-year-old girl was brought with complaints of thickening of skin of the face, upper and lower limbs. She was also having difficulty in opening of her mouth and she had a nonhealing ulcer over the lower limb. She complained of breathlessness on exertion. Physical

Figure 4 Malar rash with a typical butterfly pattern of rash sparing the nasolabial fold

*examination revealed thickened skin with presence of digital pitting scars. She had 'fish like mouth' (**Fig. 5**) and cardiac examination revealed loud P2 indicating pulmonary arterial hypertension. Investigations revealed mild anemia with mildly elevated ESR. 2D echo confirmed presence of pulmonary arterial hypertension.*

This case vignette is of diffuse cutaneous systemic sclerosis and highlights that this is just not a cutaneous disease, but disease which involves visceral organs like vasculature of pulmonary arterial tree, lungs, gastrointestinal tract, heart and kidneys. These children can have Raynaud's phenomenon.

APPROACH TO A CHILD WITH SUSPECTED VASCULITIS

Vasculitis refers to inflammation of the vessel wall. It can be divided into groups based on the predominant involvement of large, medium or small sized arteries. The large sized arteries are the aorta and its main branches. The medium sized arteries are the first level branches of aorta, namely the mesenteric, renal, splenic, and coronaries, etc. The arterioles, venules and capillaries form the small sized blood vessels. The small vessel vasculitis has been further divided into granulomatous and nongranulomatous vasculitis depending on the inflammatory pattern in the vessel wall.

Figure 5 Diffuse cutaneous systemic sclerosis with fish mouth appearance

Table 1 Organ specific manifestations of vasculitis

Organ system involved	Manifestations
• Skin	• Purpura • Tender nodules • Gangrene both superficial and deep • Panniculitis • Cyanotic hue to the extremities • Cutaneous ulcers • Livedo reticularis • Oral and nasal ulcers
• Gastrointestinal tract	• Abdominal angina • Hematochezia, melena • Intussusception
• Renal	• Hypertension • Hematuria • Proteinuria • Epididymo-orchitis
• Neurological	• Stroke • Mononeuritis multiplex • Focal neurological deficits
• Cardiac	• Myocarditis • Valvular incompetence • Myocardial ischemia • Congestive cardiac failure • Pulmonary arterial hypertension
• ENT	• Nasal ulceration • Chronic ear discharge • Subglottic stenosis • Depressed nasal bridge • Sudden onset hearing loss, vertigo
• Eyes	• Uveitis • Scleritis/episcleritis • Exudates/periphlebitis on fundal examination

When to Suspect Vasculitis?

There are general nonspecific symptoms which should raise the suspicion in any pediatrician about the possibility of vasculitis.

Table 2 Characteristics of different subgroups of vasculitis

Large vessel vasculitis	Absent pulses, claudication, congestive cardiac failure, cardiomyopathy and hypertension
Medium vessel vasculitis	Cutaneous rashes, tender nodules, hypertension, abdominal angina, orchitis, gangrene, mononeuritis multiplex
Small vessel vasculitis	Purpura, glomerulonephritis, mucosal ulcers, asthma, symptoms related to ENT

Table 3 Investigations in vasculitis

Investigation	Advantages	Disadvantages
Ultrasound and Doppler	Good for limb and neck blood vessels Cheaper No radiation Noninvasive Easily available	Poor for intra-abdominal and intra-thoracic blood vessels
Conventional angiography	Great for angiographic procedures Intramural pathology like stenosis and dilatation seen well	Invasive Contrast requirement Radiation exposure Vessel wall pathology not well seen. Hence, not useful in early stages of the disease
CT angiography	Good for large and medium sized arteries	Radiation exposure
MR angiography	No radiation Vessel wall pathology nicely seen	Overestimation of stenosis
PET scan	Useful to study the disease activity in blood vessel wall	Not good for anatomic delineation
2D echo	Useful for diagnosis of coronary artery involvement Myocarditis can be easily diagnosed	

These are fever, fatigue, malaise, weight loss, anorexia, leukocytosis, thrombocytosis and elevated ESR/CRP. There are certain organ specific features of vasculitis **(Table 1)**. It is important to take a thorough history and do a proper physical exam in any child with suspected vasculitis. **Table 2** depicts characteristics of different subgroups of vasculitis.

How to Investigate Vasculitis?

After clinical differentiation into predominant large, medium and small vessel vasculitis, the type of vasculitis will determine which type of investigation is called for to reach a diagnosis. Predominant large vessel vasculitis and medium vessel vasculitis will need to have imaging as the primary investigating tool. Histopathology is a useful tool to diagnose medium and small vessel vasculitis and not a great tool in large vessel vasculitis as the aorta and its main branches are not only difficult to biopsy but are also hazardous. Skin is the usual site from which biopsy is taken as it is easily accessible. A deep punch biopsy involving the dermis can be easily done and it helps diagnose conditions like PAN, panniculitis, SLE with vasculitic rashes, Henoch-Schönlein purpura (HSP), Wegener's granulomatosis, etc. It is important to take the biopsy from a fresh vasculitic lesion. It is wise to do immunofluorescence staining in any suspected case of HSP, SLE, and antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis **(Table 3)**.

Renal biopsy is done in those patients with abnormal urinary sediments with or without deranged renal function. Biopsies can be taken from ears, nose or throat in those patients with suspected Wegener's granulomatosis.

Management strategies in all these patients of vasculitis would include immunosupression with steroids and other immuno-suppressive agents like methotrexate, mycophenolate mofetil, cyclophosphamide, etc.

MORE ON THIS TOPIC

Cassidy JT. Textbook of Pediatric Rheumatology: Expert Consult. Elsevier Health Sciences; 2010.

Khubchandani RP, D'Souza S. Initial evaluation of a child with arthritis—An algorithmic approach. Indian J Pediatr. 2002;69:875-80.

Khubchandani RP, Viswanathan V. Pediatric vasculitides: a generalists app-roach. Indian J Pediatr. 2010;77:1165-71.

Kumar TS, Agarwal A. Approach to a patient with connective tissue disease. Indian J Pediatr. 2010;77:1157-64.

IN A NUTSHELL

1. A thorough history and a complete examination is a must in pediatric rheumatology practice.
2. All musculoskeletal complaints in children are not JIA.
3. Multisystemic involvement is common in many rheumato-logical conditions.
4. Appropriate investigations in an appropriate setting help in clinching diagnosis in most children.

Chapter 46.2
Laboratory Investigations for Rheumatological Disorders
Anju Gupta, Tapas Kumar Sabui

Pediatric rheumatology is a branch of pediatrics which can involve any organ-system unlike some organ-specific branches. It requires a detailed history and clinical examination to arrive at a diagnosis. Laboratory investigations can only help one to confirm the diagnosis and should not be used to search for a rheumatologic diagnosis. We, in pediatric rheumatology, also use many common investigations like our colleagues use in other subspecialties. In addition, we use certain investigations which are used exclusively in our field. We will be discussing these investigations in detail followed by investigations in specific rheumatologic conditions.

COMMON INVESTIGATIONS

Hemogram

Hemogram can give lots of clue to a specific rheumatologic condition. Anemia is common in many rheumatologic conditions and can occur due to anemia of chronic disease, nutritional causes due to poor appetite, and gastrointestinal losses due to nonsteroidal anti-inflammatory drugs (NSAID) and steroid therapy. Additionally, autoimmune hemolysis can be seen in conditions like systemic lupus erythematosus (SLE), where direct Coombs test may be positive. Rarely bone marrow suppression can also be seen in lupus. Leucocyte counts can both be raised or decreased in rheumatologic conditions. Autoinflammatory conditions like systemic-onset JIA (SoJIA) are usually associated with leukocytosis and thrombocytosis unless there is associated macrophage activation syndrome (MAS), when pancytopenia can be seen. Leukocytosis is far less impressive in polyarticular and oligoarticular JIA. Leukopenia and especially lymphopenia is frequently seen at presentation in lupus and is a useful sign of activity. Thrombocytopenia can be seen in lupus. Most vasculitides have thrombocytosis or normal platelet count. Thrombocytopenia generally excludes the possibility of vasculitides, only exception being Kawasaki disease, where thrombocytopenia at onset has been associated with a poor prognosis.

Erythrocyte sedimentation rate (ESR) is very commonly used in rheumatology practice. It measures the rate of sedimentation of RBC in anticoagulated blood and correlates with serum fibrinogen levels. ESR is commonly raised in most rheumatologic conditions except conditions like MAS, where ESR is low even in a setting of hyperinflammation because of falling fibrinogen level in the serum. However, it is important to remember that high ESR can be present in many infectious and malignant conditions and should definitely not be used to make a diagnosis of a rheumatologic condition. ESR trend in a given patient sometime is more helpful than a single value especially in MAS where falling ESR value is an early diagnostic marker.

Liver Function Test

Liver function tests include SGOT, SGPT, alkaline phosphatase, serum proteins and serum albumin. SGOT and SGPT elevations can be seen in many rheumatologic conditions because of liver involvement. More important than that is higher SGOT elevations than SGPT elevations, which can be seen in a setting of hemolysis or inflammatory myopathies. Serum protein and globulins can be raised in rheumatologic conditions because of inflammation. Serum albumin levels can be low again because of inflammation, malnutrition or due to renal loss because of associated nephrosis.

Coagulogram

Coagulogram can be a very useful investigation. In a child with lupus, elevated activated partial thromboplastin time (APTT) and normal prothrombin time (PT) can give a clue to presence of antiphospholipid antibodies. Both PT and APTT can be increased in hepatic involvement and more importantly, in MAS.

C-reactive Protein (CRP)

CRP concentration is less than 1 µg/dL in healthy humans, but it can increase 1000-fold following tissue injury or inflammation. CRP levels change more quickly in response to inflammation and fall quickly with appropriate treatment. After appropriate stimuli, the CRP increases within 4 hours, reaches the maximum level after 24–72 hours, and then decreases to normal values when inflammation resolves. The magnitude of inflammation is related to the magnitude of the CRP concentration. Another advantage is that CRP level is not affected, as the ESR, by the number and morphology of red blood cells and by serum immunoglobulin concentration. The CRP concentration has been shown to be superior to total white blood cells and absolute neutrophil count in predicting severe bacterial infections in febrile children. This investigation is frequently used and even over-used in rheumatology. CRP levels are raised in most rheumatological conditions, but this investigation cannot be used to differentiate these conditions from infections and malignancies, wherein CRP levels are also commonly raised. This investigation however can be used for follow-up of rheumatologic conditions. The only exception is lupus, where CRP levels are usually low during flares and a low CRP helps differentiate flares from infections in children with lupus. Children with lupus, who have arthritis or serositis at presentation, can have raised CRP, even in absence of infection. MAS usually has very impressive elevations of CRP with falling ESR. High CRP levels at the time of diagnosis have been correlated with poor therapeutic response in JIA patients.

Renal Function Tests

Renal function tests include blood urea, serum creatinine and urine examination. A good urine examination is must in rheumatology as kidney is so frequently involved in rheumatological conditions. Presence of proteinuria and microscopic hematuria can predict glomerular or microvascular involvement which is seen in SLE and many vasculitides. Blood urea and creatinine estimations can also help one know about renal involvement. Raised blood pressure and abnormal routine urine examination is a good clinical indicator of vasculitis.

Biochemistry

A fasting lipid profile showing hypertriglyceridemia can be seen in many inflammatory conditions however main use of this investigation is in identification of a life-threatening complication like MAS, when one can find significantly raised serum triglycerides. Serum ferritin levels more than 10,000 ng/mL are usually considered sine qua non for MAS, though less impressive elevations are common in most inflammatory conditions.

Radiology

In JIA, we do not use radiology as commonly as in adults to look for erosions, periarticular osteopenia and change in joint space. The reason for this is that routine joint X-rays are not very sensitive in picking up these changes early on in the disease. We use these radiographs more frequently when we are thinking of alternate

conditions in JIA like setting. Radiographs may show certain specific findings such as platyspondyly or acetabular cysts to suggest a differential diagnosis. Radiographs are also ordered in JIA children with significant deformities prior to surgery.

Chest radiographs may be useful in systemic conditions though in no setting, the findings are diagnostic of a rheumatologic condition. Chest radiographs may show features suggestive of diffuse pulmonary hemorrhage in ANCA associated vasculitis or lupus. Features of interstitial lung disease may be seen in systemic sclerosis. Chest radiographs may also point towards lung infarcts seen in antiphospholipid syndrome.

MRI is useful in evaluation of inflammatory myopathies, and sacroiliac joint involvement in enthesitis-related arthritis. Conventional or digital subtraction angiography is commonly used to assist in the diagnosis of large (Takayasu arteritis) or medium vessel (polyarteritis nodosa, Kawasaki disease) vasculitides. Small vessel vasculitides, however cannot be diagnosed based on angiography and tissue diagnosis is useful in these conditions.

Echocardiography is useful in many rheumatologic conditions, though not diagnostic in most settings. It may pick up evidence of pericardial, myocardial or endocardial involvement seen in common multisystemic diseases like SLE. It is useful to pick up coronary artery involvement in Kawasaki disease (KD). Besides characteristic coronary artery involvement, features of pericardial effusion, myocarditis or valvular involvement can also be seen in KD. Evolution of coronary abnormalities like ectasia or aneurysmal dilatation in subacute phase is considered diagnostic of KD, even when the typical clinical features are not present.

Complement Level

High C3 levels can be seen in many inflammatory conditions. Low C3 and C4 levels are common in SLE with nephritis because of complement consumption. However it is important to remember that all children with lupus do not have low complement levels.

AUTOANTIBODIES

Rheumatoid Factor (RF)

These are usually IgM antibodies directed against antigenic determinants on Fc portion of IgG. They can be detected using latex agglutination test and can be seen in many acute and chronic inflammatory conditions. Hence this test should always be repeated after 3 months of a positive test even when used in appropriate setting like polyarticular JIA in an adolescent child. Polyarticular RF positive child predicts a long course into adulthood.

Antinuclear Antibody (ANA)

ANA are autoantibodies directed against nuclear, nucleolar, or perinuclear antigens and are characteristic of autoimmune diseases. Although their pathogenetic role is not clear, ANA are suggestive of autoimmunity when they are persistently present in high titers (1:160) together with the clinical features of the disease. Positive ANA testing is associated with several inflammatory rheumatic diseases like SLE, Juvenile Dermatomyositis etc and has been included in the classification criteria for SLE, Mixed connective tissue disease (MCTD) and Sjögren syndrome. ANA can also be helpful for the diagnosis of several nonrheumatic autoimmune diseases such as autoimmune hepatitis, autoimmune thyroiditis, and drug-induced autoimmune syndromes. However, up to 20% of children who are either healthy or have benign musculoskeletal complaints have a positive ANA, and, therefore, results of ANA testing must be interpreted in combination with clinical findings.

ANA can be detected by ELISA and indirect immunofluorescence (IIF). ELISA technology dominates routine laboratory practice but tends to produce more false-positive and true weak-positive results. The *gold standard* to measure ANA is by using Hep-2 cell line of human laryngeal epithelial carcinoma for indirect immunofluorescence. Both the titer and pattern of the nuclear antigen are studied. The pattern of ANA staining on IF reflects the specific nuclear antigens to which the ANA is binding. However, using the ANA pattern to diagnose specific autoimmune disorders has low sensitivity and specificity. Hence if ANA is positive in an appropriate setting, one should try to conform it with antibodies to extractable nuclear antigens (ENA) using more specific tests such as the double-immunodiffusion assays, the immunoblot test, and ELISA.

The homogeneous pattern of ANA is due to the presence of antihistone and/or anti-dsDNA antibodies that are highly specific of SLE; however the presence of anti-dsDNA may also result in a peripheral or rim pattern. The speckled pattern is associated with anti-Sm (anti-Smith antigen), anti-SSA, and anti-SSB antibodies of Sjögren's syndrome and MCTD. The nucleolar pattern is related to anti-Scl70 antibodies in systemic sclerosis, and the centromere pattern is seen with antibodies to the kinetochore in the CREST (Calcinosis, Raynaud's phenomenon, Esophageal disease, Sclerodactyly, Telangectasia) syndrome and in primary biliary cirrhosis. ANA is frequently positive in pauciarticular JIA seen in young girls and does not predict development of lupus. Instead, it is associated with a high risk of chronic blinding uveitis.

Anti-ds DNA though not very sensitive, is moderately specific for SLE. Anti-ds DNA levels have been found to correlate with disease activity, and hence can be used to monitor the disease. Coming to specific antibodies to ENA, anti-SSA and anti-SSB antibodies are found in SLE and Sjögren's syndrome. The importance of these antibodies in SLE lies in a high chance of neonatal lupus with congenital heart block in the offspring of a mother with lupus. Anti-RNP antibody is classical of mixed connective tissue disease. Anticentromere antibodies are usually associated with the CREST syndrome. Anti-Scl-70 antibody is found in scleroderma and at low frequency in the CREST syndrome. Anti-Sm antibody is said to be a highly specific marker for SLE, though occurs in a small minority. Anti-histone antibodies are usually seen in drug induced lupus.

ANCA (Anti-neutrophil Cytoplasmic Antibody)

There are different kinds of ANCA. ANCA with cytoplasmic staining (cANCA) and ANCA with perinuclear staining (pANCA) are most important. Wegener's granulomatosis (WG) is mostly associated with cANCA, which is mostly directed against proteinase 3 (PR3), while pANCA directed against myeloperoxidase is mostly associated with microscopic polyangiitis (MPA). ANCA tests use either indirect immunofluorescence (IIF) or ELISA technique. IIF tests are more sensitive, but less specific than ELISA and are operator dependent. They can be quantified as dilution titers. Commercial ANCA ELISAs have not been standardized and vary in their sensitivity and specificity.

Antiphospholipid Antibodies

Anticardiolipin (aCA), antibeta 2 glycoprotein 1 (aβ_2GP1) and lupus anticoagulant (LAC) are commonly used. Presence of one or more of these antibodies in association with thrombosis confirms the diagnosis of antiphospholipid syndrome in children. It is commonly seen in association with rheumatologic conditions like lupus. The importance of identifying this syndrome lies in a high risk of recurrence of thrombosis, both arterial and venous. All children with lupus must be evaluated for these antibodies at the time of diagnosis and periodically thereafter, even in the absence of thrombosis.

TISSUE DIAGNOSIS

Biopsies of various tissues are useful in rheumatologic diagnosis in appropriate setting. Renal biopsy is useful in a child presenting

with nephrotic syndrome, nephritis, and rapidly progressive glomerulonephritis, which are the most common renal presentations of rheumatologic conditions. Histopathology along with immunofluorescence would help in distinguishing lupus from vasculitic group of disorders like AAV, HSP nephritis, etc. Muscle biopsy is occasionally used in inflammatory myopathies when typical skin manifestations are not obvious or diagnosis is in doubt. Tissue biopsies like kidney, lung, muscle, etc are useful in diagnosis of vasculitis group of disorders. Skin biopsy in HSP shows leucocytoclastic vasculitis with IgA deposition on immunofluorescence.

SPECIFIC RHEUMATOLOGIC CONDITIONS AND ROLE OF LABORATORY INVESTIGATIONS

Juvenile Idiopathic Arthritis (JIA)

Diagnosis of JIA is largely clinical; however certain investigations can be used to define the broad groups. These investigations include ANA, rheumatoid factor, HLA-B27 and radiologic examination. ANA is commonly positive in pauciarticular JIA seen in young girls and has strong association with development of uveitis. Rheumatoid factor, on the other hand, is seen in older girls with polyarticular JIA and predicts a longer course. HLA-B27 is positive in oligoarticular JIA in older boys. Role of radiologic examination lies in seeing periarticular changes in chronic arthritis. More important than that is to pick up mimickers of JIA like skeletal dysplasia and certain genetic conditions like camptodactyly-arthropathy-coxa vara-pericarditis syndrome.

SLE

Systemic lupus erythematosus typically is a multisystem illness and hence may need investigations related to various systems. Besides involvement of various systems, autoantibodies are useful in diagnosis. ANA is positive in more than 95% children with SLE and with better techniques, ANA negative lupus is said to be almost nonexistent. Only if ANA is positive, should one try to go in for specific autoantibodies. Anti-dsDNA antibodies and low complement levels are useful in predicting disease activity.

Inflammatory Myopathies

Laboratory support for diagnosis of inflammatory myopathies can be divided into the following categories: muscle enzymes, autoantibodies and other supportive tests like histopathology, MRI and neurophysiology.

Muscle Enzymes

These remain the most commonly used tests to diagnose muscle injury. The common enzymes employed are creatine kinase (CK), aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), lactate dehydrogenase (LDH) and aldolase. CK is the most common enzyme used and in elevated in >90% children with Juvenile dermatomyositis. CK is the most sensitive enzyme and may be the only enzyme which is increased in mild cases. An increase in CK after an initial decrease on therapy may predict a relapse. However CK does not correlate well with muscle strength and may be normal in advanced muscle disease. Other enzymes like SGOT, SGPT, LDH and aldolase can be used, however these enzymes have far wider distribution in body and hence can be increased in many more conditions. Though SGOT elevations are far more impressive than SGPT elevations in JDM, SGPT can be raised and should not prompt one not to initiate methotrexate.

Autoantibodies

ANA is positive by indirect immunofluorescence in 50–80% patients with JDM. In high titers, it helps to rule out other causes of myopathies where skin manifestations are not characteristic. Usual patterns of ANA are nuclear speckled and pure cytoplasmic staining without nuclear staining. Certain muscle specific and muscle associated autoantibodies have been used in research settings however they are usually not useful for making a diagnosis or monitoring response. Antibodies to signal recognition peptide have been found to be associated with poor response to steroids and a more severe disease course. Anti-Mi-2 antibodies, in contrast, have been associated with a benign course, distinctive rash and a good response to steroids.

Neurophysiologic Studies

Electromyogram (EMG) can help in confirming the diagnosis of JDM, however is usually not needed unless clinical features are doubtful. The characteristic EMG features comprise changes of myopathy and denervation.

Histopathology

Muscle biopsy is one of the five diagnostic criteria given by Bohan and Peter, however is now only done if clinical features are in doubt. Muscle involvement can be spotty, hence a prior MRI study to determine involvement of muscle can be used to increase the yield of this investigation.

Radiology

MRI has been used far more commonly in the past two decades, because of its noninvasive nature. T1-weighted images can pick up fibrosis, atrophy and fatty infiltration whereas T2-weighted images with fat suppression can show muscle edema and inflammation. MRI has also been used to monitor therapy and predict future relapses.

Kawasaki Disease

Investigations in this disease can be divided into two main categories: one to show inflammation and the other to pick up coronary involvement. Inflammation is accompanied by anemia, leukocytosis, raised ESR and CRP, sterile pyuria, and hypo-albuminemia in the acute phase. Ultrasonographic evidence of gall bladder hydrops occurs due to acalculous cholecystitis in acute phase. Thrombocytosis is usually seen in second and third week of illness and can support the clinical diagnosis. Echocardiographic examination is a must to pick up coronary abnormalities in the form of ectasia or aneurysmal dilatation. This examination helps in predicting need of thromboprophylaxis with low dose aspirin, low molecular weight heparin or oral anticoagulants in children with giant aneurysms. CT or conventional angiography may help in better delineation of giant aneurysms and complications like stenosis or calcifications.

Henoch–Schönlein Purpura (HSP)

Though the diagnosis of HSP is largely clinical, a skin biopsy showing leucocytoclastic vasculitis with IgA positivity on immuno-fluorescence supports the diagnosis. Usually no more investigations are needed except a urine examination to pick up evidence of nephritis. Some children with nephritis may need kidney biopsy for prognostication and decision regarding immunosuppression.

Takayasu Arteritis

Once this disease is suspected, the gold standard for diagnosis is angiography. Prior to going in for angiography, investigations like

ultrasound to look for kidney size, Doppler to look for stenosis and echocardiography to look for cardiac dysfunction are useful. Unilateral renal artery stenosis may present with discrepancy in renal size, whereas bilateral stenosis may not show this discrepancy. Doppler of renal and carotid arteries is useful in picking up abnormal flow related to stenosis, however it may be difficult to visualize aorta with this modality. Echocardiography may show evidence of cardiac dysfunction.

Conventional angiography or digital subtraction angiography are the gold standards for diagnosis. The vascular imaging shows intra-arterial disease-related damage like occlusion, stenosis (which is usually proximal and ostial), dilatation, and aneurysms. Usually there is contiguous involvement of arteries however skip lesions may be seen. What conventional angiography does not show is the status of vessel wall itself. Inflammatory disease activity in the vessel wall may be better seen with CT or MR angiography, however these modalities have still not become standard of care.

Of late, PET scan has been used to detect inflammation in arterial wall. It is based on the principle of excessive glucose metabolism by inflammatory cells. However, it is expensive, and is associated with a significant radiation dose. Moreover, this investigation really needs to prove itself both for diagnosis and monitoring before becoming the standard of care.

Polyarteritis Nodosa (PAN)

Conventional angiography is the gold standard investigation for PAN. Tissue biopsies may be useful in case angiography is not suggestive.

Antineutrophil Cytoplasmic Autoantibody Associated Vasculitis (ANCA Associated Vasculitis)

ANCA associated vasculitides (AAV) although rare do occur in children, but less commonly than PAN. AAV can be sub-classified into WG, MPA, and renal limited vasculitis. These diseases are characterized by vasculitis predominantly of the small blood vessels with few or no immune deposits associated with circulating ANCA and are diagnosed from their different clinical presentations. The diagnosis of primary systemic vasculitis is built on a compatible pattern of clinical features supported by specific serological (or radiological) investigations and confirmatory biopsy. An essential addition is the exclusion of other causes of the clinical presentation, of mimics of vasculitis and of secondary causes of vasculitis.

IN A NUTSHELL

1. Laboratory investigations in pediatric rheumatology should be used judiciously.
2. Simple investigations like hemogram, CRP, liver function test, renal function test and urine examination can give clues to rheumatological conditions.
3. ANA should be done by indirect immunofluorescence and a significantly positive ANA test should be followed by estimation of antibodies to extractable nuclear antigens.
4. Large and medium vessel vasculitis usually need vascular imaging for diagnosis whereas small vessel vasculitis needs histopathological examination.

MORE ON THIS TOPIC

Atkinson JP. C-reactive protein: a rheumatologist's friend revisited. Arthritis Rheum. 2001;44:995-6.

Batlivala SP. Focus on diagnosis: the erythrocyte sedimentation rate and the C-reactive protein test. Pediatr Rev. 2009;30:72-4.

Kumar Y, Bhatia A, Minz RW. Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited. Diagn Pathol. 2009;4:1.

O'Sullivan M, McLean-Tooke A, Loh RK. Antinuclear antibody test. Aust Fam Physician. 2013;42:718-21.

Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111:1805-12.

Pipitone N, Versari A, Hunder GG, Salvarani C. Role of imaging in the diagnosis of large and medium-sized vessel vasculitis. Rheum Dis Clin North Am. 2013;39:593-608.

Siegel DM. Antinuclear Antibody (ANA) Testing. Pediatr Rev. 2003;24:320-1.

Targoff IN. Laboratory testing in the diagnosis and management of idiopathic inflammatory myopathies. Rheum Dis Clin North Am. 2002;28:859-90.

Wiik AS. Autoantibodies in ANCA-associated vasculitis. Rheum Dis Clin North Am. 2010;36:479-89.

Chapter 46.3
Juvenile Idiopathic Arthritis
Sujata Sawhney

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children with a quoted prevalence of 1: 1000. It is thus not a very common disease, but has a potential for disability and long-term morbidity if not treated in time. The single most important factor that guides the long-term prognosis of these children is the "time to remission from disease onset". This in turn is dependent on early recognition and appropriate referral where indicated. This chapter is aimed to assist the clinician to diagnose these children in the clinic and to provide the best therapeutic pathways to manage these patients.

DEFINITION AND NOMENCLATURE

There have been many different terminologies that have described juvenile arthritis in children in the past such as juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA). These have been largely superseded by the term JIA. JIA is the current term that is used to describe arthritis in a child that begins under the age of sixteen, lasts for more than 6 weeks and where other causes have been excluded. This classification scheme was put forward by the International League Against Rheumatism (ILAR). The primary goal of the ILAR classification has been to identify as far as possible, clinically and biologically homogenous groups of children with chronic arthritis. This is an essential first step towards further research to elucidate pathogenetic mechanisms of these conditions. This classification system that has been proposed is for research purposes where homogeneity and exclusivity are the hallmarks. The ILAR further subdivides children with JIA into seven discrete categories (**Table 1**). It is important to note that in India, the percentage prevalence of the subcategories of JIA is very different from that seen in the West. Enthesitis related arthritis (ERA) and systemic onset JIA (SoJIA) are 75% of the JIA patients in India, and in the West it is oligoarticular JIA (OJIA) which constitutes up to 60%. There are several important features of the ILAR that deserve specific mention:

- The term JIA describes a very heterogeneous group of clinical cases
- Each subcategory of children is mutually exclusive
- The subcategory can change over time, e.g., if a child has three swollen joints at 4 months of disease (OJIA) and seven swollen joints at 7 months of disease, he would be reclassified as extended oligoarthritis
- No test can rule in or rule out the disease and there are no explicit guidelines for laboratory testing in this schema
- No radiological classification features have been included for the spinal inflammatory component of ERA
- There have been several criticisms of this classification system and it is possible that over the next few years, modifications are seen. As an example, it has been suggested that the ANA (Antinuclear antibody) positive status is a better descriptor of homogeneity and that oligo or polyarthritis is an arbitrary division.

CLINICAL APPROACH AND PRESENTATION

Arthritis is defined as a swollen joint or a joint which has a painful range of movement. Just as there are many causes for pyrexia, similarly there are many reasons for children to have arthritis. Moreover, arthritis has to be differentiated from noninflammatory mechanical aches and pains. A careful history, examination and few structured investigations can help the physician.

History

Four questions need to be answered up front:
1. Is the pain inflammatory or noninflammatory?
2. Is the complaint acute or chronic (> 6 weeks)?
3. Is it one joint that is involved or are there more?
4. Is the complaint only articular or are there any extraarticular features as well?

Table 1 International League Against Rheumatism (ILAR) classification for Juvenile idiopathic arthritis (JIA)

Sub category	Key features	Exclusions *
Systemic arthritis (SoJIA)	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following: Evanescent (nonfixed) erythematous rash, Generalized lymph node enlargement, Hepatomegaly and/or splenomegaly, Serositis	a, b, c, d
Oligoarthritis (OJIA) Persistent Extended	Arthritis affecting one to 4 joints during the first 6 months of disease Affecting not more than 4 joints throughout the disease course Affecting a total of more than 4 joints after the first 6 months of disease	a, b, c, d, e
Polyarthritis (RF negative) (PJIA)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF positive) (PJRA)	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive	a, b, c, e
Enthesitis related arthritis (ERA)	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first degree relative	a, d, e
Psoriatic arthritis (PSoJIA)	Arthritis and psoriasis, or arthritis and at least 2 of the following: Dactylitis, Nail pitting or onycholysis, Psoriasis in a first-degree relative	b, c, d, e
Other arthritis Fits no category Fits more than one category	Arthritis that fulfills criteria in no category or in 2 or more of the above categories	-----

* Exclusions for JIA categories
a Psoriasis or a history of psoriasis in the patient or first degree relative.
b Arthritis in an HLA-B27 positive male beginning after the 6th birthday.
c Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.
d The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
e The presence of systemic JIA in the patient.

Is the Pain Inflammatory or Noninflammatory?

This is a simple question that can be well answered on careful history taking. Inflammatory joint pain (e.g., pain seen in JIA) is more in the morning, there is the phenomenon of early morning stiffness or gelling for more than 30 minutes; there is usually an associated swelling of the joint, the patient improves with gentle mobility and worsens with inactivity. Contrast this to the patient with noninflammatory pains (e.g., hypermobility), the child has no early morning pain/stiffness, no joint swelling, the patient improves with rest and worsens with activity.

Is the Complaint Acute or Chronic (> 6 Weeks)?

For all practical purposes, there are four important and common reasons for an acutely swollen single joint: sepsis, acute reactive arthritis, trauma and hemarthrosis. The abrupt swelling of a joint in hours suggests an infectious cause or a bleed. Acute presentation of polyarthritis is usually seen in reactive arthritides or as an acute presentation of a chronic disease such as JIA. Thus, preceding history of diarrhea, dysentery, urethritis, rashes, conjunctivitis and tonsillitis is important. JIA usually presents as chronic arthritis with inflammatory joint complaints lasting for more than 6 weeks.

Is it One Joint that is Involved or are there More?

It is important to ask for the history of the number of joints involved and always remember to examine all the joints as the patient may only complain of the most troublesome joint. The number of joints involved is important as it leads one to the correct differential diagnosis.

Is the Complaint Only Articular or are There Any Extra-articular Features?

Arthritis can occur in most rheumatologic diseases from JIA to connective tissue diseases and also in several forms of vasculitis. Thus, it is important to take a detailed history of the patient with a focus on the rheumatologic complaints to tease out features that suggest a connective tissue disease, systemic vasculitides, infection, malignancy or other mimics of JIA such as skeletal dysplasia.

Examination

A thorough top to toe examination is needed for all patients with an emphasis on growth, detailed systems review and joint examination. For a quick screen of the musculoskeletal system, the reader is referred to pGALS (Pediatric Gait Arms Legs and Spine) system of examination that is available on U-tube. Once an abnormality is found, the joints can be examined individually by inspection, palpation and movement, the latter should be both active and passive. Children with JIA have warm swollen joints with tenderness on movement (**Figures 1** and **2**). The joints in this condition are not acutely painful and are not erythematous.

Nonarticular

Growth parameters, stigmata of connective tissue disease such as photosensitive rashes, Raynaud phenomenon, mucositis, oral ulcers, lymphadenopathy, organomegaly and alopecia should be looked for. Features of vasculitis such as hypertension, skin rashes, asymmetric pulses and mononeuritis multiplex are important. Clinical examination should also look for bony tenderness and periarthritis to exclude malignancy in children who have marked pallor, severe night pains, weight loss and loss of appetite.

Eye Examination

Eye examination deserves a special mention as uveitis can afflict child with JIA, especially children with ANA positive disease and ERA patients. The ANA positive preschooler with OJIA has a high risk (60%) of developing silent anterior chronic uveitis that is painless, yet the eye can go blind if the child is left untreated. The second category of children with JIA to get uveitis is the ERA patient who develops an acute painful red eye that is usually not scarring. This examination should be done on a slit lamp by a skilled ophthalmologist.

Articular Examination

All joints should be examined and documented carefully. The joint examination needs skill and experience and should be thorough as the pattern of disease is critical to make the diagnosis. On completing the examination, the clinician should be able to confirm the number of joints that are swollen, and tender and describe the pattern as predominant upper or lower limb disease, symmetric or asymmetric, large or small joint and involvement of axial skeleton.

Severe growth failure, systemic disease, hypertension, vasculitic rashes, severe joint pain and tenderness, joint erythema, predominant periarthritis in children with swollen joints *points away* from the diagnosis of JIA. On completion of the history and detailed examination, the clinician is armed with 95% detail needed to reach a diagnosis and with this, he is able to recognize a pattern and decide if the child has JIA or a mimic. There are several details that are needed in the history and examination to recognize a pattern of the disease in JIA. These are discussed in **Table 2**.
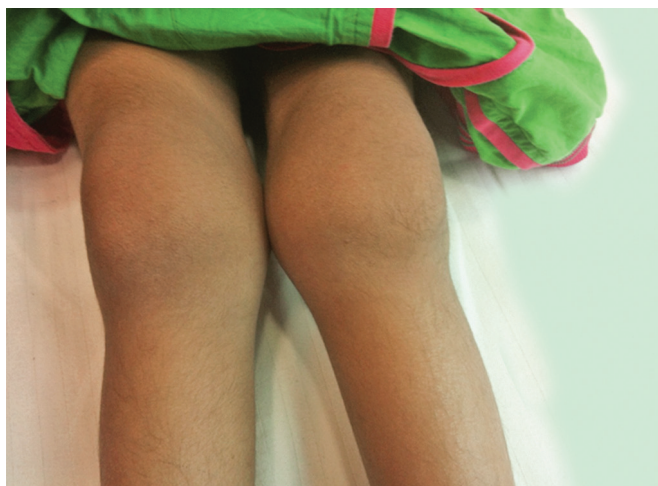
Figure 1 Arthritis of both knees

Figure 2 Arthritis of proximal interphalangeal joints

Table 2 Pattern recognition of subcategories of Juvenile idiopathic arthritis (JIA)

Subcategory	Usual age of presentation	Sex predilection	Prevalence in India (%)	Typical pattern	Differential diagnosis
SoJIA	Any	F = M	30	Daily spiking fever, well between fever spikes, large and small symmetrical joint disease	Infections, malignancies and connective tissue diseases
OJIA both persistent and extended	< 5 years	F > M	10	Preschool, female with asymmetric, large joint involvement, most common knee. Small joint suggests progression. Isolated upper limb joint disease unusual	With monoarthritis, consider tuberculosis, hemophilia, pigmented villonodular synovitis. Other JIA subtypes, e.g., psoriatic
PJIA RF negative	Two peaks : 1–3 years, and adolescence	F > M	10	Symmetric small and large joint disease	CTDs, vasculitis, reactive arthritides
PJIA RF positive	9–11 years	F > M	05	Symmetric small and large joint disease	CTDs, vasculitis, reactive arthritides
ERA	Adolescent	M > F	40	Several patterns: asymmetric predominant large and small joint disease of lower limbs, midfoot disease, enthesitis, axial involvement, any combination of the above	In India, often misclassified as oligo JIA. HLA-B27 positive in > 95%. With fever misclassified as SoJIA
Psoriatic arthritis	Two peaks: preschool and adolescent	F > M	2	Two patterns: preschool with large joint and dactylitis. Older with enthesitis and axial involvement	OJIA and ERA, in India with dactylitis tuberculosis
Others/unclassifiable	Any	F = M	3	Does not have any particular pattern, usually family history of psoriasis in a child who has, e.g., OJIA makes the child unclassifiable	All categories of JIA

Abbreviations: JIA, Juvenile idiopathic arthritis; SoJIA, systemic onset JIA; OJIA, oligoarticular JIA; HLA, Human leukocyte antigen; PJIA, polyarticular juvenile idiopathic arthritis; RF, rheumatoid factor; CTD, connective tissue diseases; ERA, Enthesitis related arthritis.

Investigations

Laboratory tests are important tools that help to support the diagnosis of JIA, evaluate the disease activity, monitor the side effects of therapy, and also assist the physician to exclude rheumatologic mimics.

Complete Blood Count

The complete blood count (CBC) evaluation is a routine at first visit and subsequently every 12 weeks for disease and drug monitoring. The hemoglobin may be mildly low, WBC high with neutrophilic predominance and platelet count high in SoJIA patients. A low WBC count with new onset disease suggests an alternative diagnosis. Similarly, thrombocytopenia suggests an alternative diagnosis or heralds the onset of macrophage activation syndrome or drug toxicity.

Acute Phase Reactants

Erythrocyte sedimentation rate (ESR) is a measure of the elevated levels of fibrinogen and other plasma proteins which increase in inflammation. High values of ESR indicate ongoing inflammation. The ESR is employed as a part of several outcome measures used to assess disease activity in JIA. PJIA, ERA and SoJIA patients may have significant increase in the ESR. **C-reactive protein (CRP)** is another acute phase reactant which rises early and normalizes rapidly. **Serum ferritin** is elevated in SoJIA and macrophage activation syndrome. Phagocytic macrophages are an important source of ferritin. High serum ferritin is not included as a diagnostic criterion for SoJIA.

Immunologic Tests

Rheumatoid factor (RF) consists of immunoglobulin antibodies of the IgM class directed against the Fc (constant) region of the

Figure 3 Magnetic resonance imaging showing sacroiliitis

native immunoglobulin G molecule. Less than 5% of patients with JIA are RF positive. It is a prognostic and not a diagnostic test for JIA. *ANA* is commonly positive (60%) in OJIA patients and is associated in this subset with a high incidence of uveitis. It is also positive in low titers in 2–15% of normal children. Human leukocyte antigen (HLA) B27 is class I surface antigen encoded by the B locus in the MHC on the short arm of Chromosome 6. It is positive in over 90% of children with ERA. Liver and renal function tests are done to monitor the adverse effects of drug treatment. X-rays, MRI (**Figure 3**) and bone scan, as appropriate, are useful in doubtful cases.

DIFFERENTIAL DIAGNOSIS

The diagnosis of JIA is clinical, one of exclusion and cannot be confirmed by any laboratory test. Important differentials that should be excluded are infections, connective tissue diseases, vasculitis and malignancies. Any child who does not fit into a classical disease pattern of each subcategory should be evaluated carefully for alternative diagnosis.

MANAGEMENT

The aims of good management of JIA are divided into short- and long-term goals (**Box 1**). These aims can be fulfilled if the child with inflammatory joint disease has access to a multidisciplinary team with inputs from a pediatric rheumatologist, who will liaise with the local general pediatrician, ophthalmologist, nurse specialist, physiotherapist, occupational therapist, orthopedic surgeon and clinical psychologist. The challenge in our country is to identify the team members under one roof and ensure that the child has a practical and comprehensive care pathway.

Objective Assessment
- Assess disease activity in children with JIA.
- Define inactive disease and remission.

Outcome Measures
Outcome measures are used for children with JIA, more for clinical trials than in day to day clinical practice. These are critical objective parameters designed to judge whether or not the patient has improved. "The definition of improvement" is used to assess disease response. This definition employs a core set of 6 response variables: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of "active" joints (joints with swelling, not due to deformity or joints with limitation of motion and with pain, tenderness, or both), number of joints with limitation of motion, functional ability by a validated test, and ESR. To meet the definition of improvement, at a scheduled visit, the patient should have a 30% improvement from baseline in at least three of the six response variables, and worsening of 30% or more in no more than

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BOX 1 Aims of management of JIA

Short-term Goals
- Try and achieve complete disease control in the shortest possible time period.
- Patients should be stratified even in their particular subcategories. For example, an oligoarticular patient with a painful knee contracture who is not bearing weight cannot be treated with the same medications as an OJIA patient with a relatively painless knee swelling who is bearing weight well but has aggressive uveitis. Thus the therapy must be individualized.
- Preserve vision in the child with ANA positive oligoarthritis and uveitis. This subgroup of children is found in India and standard screening for uveitis is essential and must be built into the care plan of these children.
- Prevent pain and discomfort.

Long-term Goals
- Maintain the child in complete disease control
- Prevent joint destruction and deformities
- Promote growth and development
- Ensure psychological well being
- Carefully follow radiological disease progression to follow erosive disease changes
- Limit side effects of drugs
- Rehabilitate the child with deformities

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one of the six response variables. These improvements are similar to the American College of Rheumatology (ACR) 30/50/70 for adult Rheumatoid Arthritis.

Juvenile Arthritis Disease Activity Scores (JADAS)
This is a composite disease activity score for JIA. It includes four measures: (1) physician global assessment of disease activity; (2) parent/patient global assessment of well-being; (3) active joint count, and (4) ESR. A score of 0–57 is given for a 27 joint count. It has revealed strong responsiveness to clinical change which is not true for the Childhood health assessment questionnaire (CHAQ). This may be used as a standard tool in the clinic over the next few years. Cut-off values have been proposed to match inactive disease. A cut off of 1 equates inactive disease.

Remission/Inactive Disease
Two types of clinical remission are described.

Inactive disease is the term used for children with JIA who have no active arthritis, systemic features or uveitis, normal ESR and a physician score that suggests no active disease.

Clinical remission on medication is the presence of inactive disease for 6 months on medication.

Clinical remission off medication is the term reserved for children with JIA who have inactive disease for 12 months after discontinuing all medications.

These are important concepts as children often flare during the course of their disease and over the long-term, it is possible to see the time they have spent with inactive disease. In fact, in newer trials in pediatric rheumatology such as the Trial of early aggressive therapy in polyarticular JIA (TREAT) trial, inactive disease has been used as primary end point underscoring the importance of no disease versus improvement as defined by ACR-PEDI 30/50/70 described above. Thus, the principle of management of children with JIA is early aggressive treatment with a "T2T" approach: treat to a target of remission as defined above.

Medications

There are basically four modalities of treatment that can be used to treat children with JIA. They are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, Disease modifying anti rheumatic drugs (DMARDs) and Biologic reaction modifiers (BRMs). BRM include antitumor necrosis factor agents (Etanercept and Infliximab), anti-Interleukin 6 (Tocilizumab), anti CD20 (Rituximab) and T cell co-stimulatory blockade (Abatacept). The availability of BRMs in India and abroad has completely changed the outlook for many children with JIA. The main constraint in our country is the cost.

Oligoarticular JIA
Mild disease can be treated with NSAIDs or intra-articular steroids. DMARDs are recommended for this group for difficult to control uveitis or when damage to a critical joint threatens function (wrist/hip) or in extended OJIA.

Polyarticular JIA
A patient with mild disease can be treated with NSAIDs and hydroxychloroquine (HCQ at a dose of 5–6 mg/kg/day). A vast majority of children will need methotrexate. Low dose steroids which are tapered over a few months are very useful in many patients and the benefits outweigh the risks. Tumor necrosis factor (TNF) antagonists are reserved for methotrexate resistant patients. It should be noted that if the child does not show significant improvement on objective disease assessment in three months or has not achieved remission in six months, BRMs must be given. The most common agent to be used is Etanercept.

Systemic Onset JIA

This group of patients can have several presentations: there are some children with raging fevers and barely discernable arthritis, others with severe arthritis and then a group that has a life threatening condition called macrophage activation syndrome where the child with SoJIA develops high grade continuous fever, a marked drop in the platelets and ESR and features of coagulopathy.

- A child with very mild disease may improve with NSAIDs alone over a period of a few weeks. Most commonly used NSAID is naproxen at a dose of 15–20 mg/kg/day in two divided doses.
- A vast majority of the children will require steroids that can be given orally at a dose of 1–2 mg/kg/day and then slowly tapered off over a period of months or even IV methyl prednisolone at a dose of 30 mg/kg/day, maximum 500 mg given daily for 2–3 days.
- Methotrexate (10–25 mg/m^2 weekly) has a good effect on the arthritis but its role in reducing the systemic features of this condition is not well understood.
- Thalidomide may be used in the resistant patient where it controls both the arthritis and the systemic features.
- The biologic agents used in this subcategory are Anakinra and Toculizumab; TNF blockers have the least efficacy in this subcategory.
- Cyclosporine (4–5 mg/kg/day in two divided doses) has a dramatic effect in children with macrophage activation syndrome and may also be used to control systemic features in the difficult to control patients.

Enthesitis-Related Arthritis

The components of this disease that need attention are acute anterior uveitis, peripheral joint disease, enthesitis and axial joint disease. If the patient has less than four peripheral joints without critical joint involvement such as hip disease, they may be treated with NSAIDs and intraarticular steroids. With hip joint disease, most children would get methotrexate as for polyarticular disease. Sulfasalazine is also effective in these patients. With axial disease, the child would need regular NSAIDs for a prolonged time. If there is no improvement in 3 months, TNF blockers should be used. Acute uveitis may be treated with topical steroids, and in recurrent uveitis, the child will benefit with long-term methotrexate or Infliximab.

Psoriatic Arthritis

Asymmetric disease of small joints especially the distal interphalangeal (DIP) joints and dactylitis are characteristic of psoriatic arthritis. Significant nail pitting often precedes arthritis. The skin and joint disease may not always follow the same course. In addition to local skin treatment, NSAIDs/intraarticular steroids are used for localized disease involving a few joints, and methotrexate is used for aggressive disease involving multiple joints.

American College of Rheumatology (ACR) Guidelines for the Management of JIA

The ACR has chosen to describe the pathways of care for five groups of children: (1) oligo disease; (2) poly disease; (3) SoJIA with systemic features; (4) SoJIA with articular disease; and finally, the child with axial disease. Each category of disease has been divided into low, moderate and high disease activity and poor prognostic markers have been listed for each category. The guidelines are heavily weighted in favor of use of biologics within 3–6 months of ongoing disease in most categories which is not practical for the majority of Indian children with JIA.

Growth

Significant chronic disease in childhood often impacts the growth in children and thus all children with JIA should have periodic assessment of their height velocity. The best strategy to maximize growth is aggressive disease control, nutritional support and judicious yet minimal use of steroids.

Deformities

Children with arthritis have a growing skeleton and are vulnerable to developing deformities and flexion contractures early on in the disease process. Early appropriate multidisciplinary team management is the answer to these issues.

Osteoporosis

There are many factors that adversely affect bone mass in children with JIA. Active arthritis and medications used in arthritis, especially steroids also have a known osteopenic effect. Decreased physical fitness and participation in organized sport, in addition to poor vitamin D and calcium intake contribute to the low bone mineral density (BMD). The following strategies are generally employed to optimize bone mass in children with JIA: aggressive control of disease activity, avoidance of corticosteroid use, and optimizing physical activity and calcium intake. Bisphosphonates have been recently shown to be effective in treating secondary osteoporosis in JIA. This drug crosses the placenta and is highly teratogenic. It is thus mandatory for patients to avoid pregnancy during the duration of treatment and for up to six months after discontinuation. Finally, growth hormone also improves the growth retardation and osteoporosis, particularly where the disease is stable but not in remission.

Uveitis

Standard treatment of uveitis is the use of topical methyl prednisolone and mydriatics to prevent synechiae. Methotrexate and other DMARDs have been tried; benefit is seen with methotrexate at higher doses (15–30 mg/m^2 weekly), when used subcutaneously. Recently, it has been shown that infliximab is effective in treatment of uveitis.

When should methotrexate be stopped? There is paucity of published data to support evidence-based decisions in this area. Most authors suggest that discontinuation of methotrexate when treatment induced remission has persisted for less than 1 year, frequently results in return of arthritis within 6 months of drug discontinuation. NSAIDs and other medications are discontinued prior to attempting withdrawal of methotrexate.

Schooling

Attending school full time and participating in all school activities are achievable goals in all children. It is important that the disease be in remission so that the child has the opportunity to attend regular full time school which will serve two purposes: education and peer interaction which in turn help to make the child a balanced adult.

Psychological Issues, Disease Education and Compliance

This is as important as the medical care; and is given for a long time and includes visits to the doctors, therapists and blood tests. The child should be strongly encouraged to attend school regularly and children should determine their own level of activity. Disease education which is culturally appropriate must be built into the care plan of the child with arthritis. Psychological assessment for the child with chronic disease is a routine process in the western world, but is not common place in India. Compliance with hospital visits, drug intake and following exercise regime are issues that must be addressed periodically.

PROGNOSIS

The prognostic criteria are not well defined for JIA. Some features such as young age at onset, positive rheumatoid factor, long duration of elevated ESR and polyarthritis do predict ongoing disease activity at follow-up. Schneider et al studied children with SoJIA and suggested that children who at six months of disease had persistent systemic features and a platelet count of more than six lakhs were likely to have severe destructive arthritis and a poor functional outcome. Data from India suggest that after a median follow-up of 10 years, up to 60% of patients have active disease. Certainly, a major contributor here is delayed referral and delayed institution of disease modifying agents.

Transition of the Adolescent with JIA to Adult Care

Juvenile idiopathic arthritis is a chronic disease, with a third of patients carrying the disease into their adult years. Delayed adolescence both physically and emotionally is being recognized more widely and adolescent centered services to aid transition to adulthood have a major role to play in the long-term care of the patient with JIA. Transition to adult care is a process that begins in the adolescent age. Attention to vocational skills, independent living skills, and self-advocacy warrant careful care and planning. Compliance with the treatment regimen including medication, blood monitoring, exercises, splint usage and regular visits to health professionals are demanding on the child and family.

MORE ON THIS TOPIC

Kahn P. Juvenile idiopathic arthritis: an update on pharmacotherapy. Bull NYU Hosp Joint Dis. 2011;69:264-76.

Kunjir V, Venugopalan A, Chopra A. Profile of Indian patients with juvenile onset chronic inflammatory joint disease using the ILAR classification criteria for JIA: a community-based cohort study. J Rheumatol. 2010;37:1756-62.

Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol. 2003;30:1900-03.

Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol. 1998;25:1991-4.

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.

Sawhney S. Juvenile idiopathic arthritis: Classification, clinical features, and management. Ind J Rheumatol. 2012;7(Suppl):11–21.

IN A NUTSHELL

1. Juvenile idiopathic arthritis is the most common rheumatic disease in children with a quoted prevalence of 1:1000.
2. JIA is categorized into seven subtypes and each patient should have an individualized care plan that would depend on the disease subtype, burden of disease and prognostic factors.
3. Majority of mild disease may be treated with NSAID and/or intra-articular steroid. Moderate-to-severe disease will need methotrexate. TNF antagonists are reserved for the methotrexate resistant patients. It should be noted that, if the child does not show significant improvement on objective disease assessment in 3 months or has not achieved remission in 6 months, biologic reaction modifiers (BRMs) must be given.
4. Biologic reaction modifiers include antitumor necrosis factor agents (Etanercept and Infliximab), anti-Interleukin 6 (Tocilizumab), anti CD20 (Rituximab) and T cell co-stimulatory blockade (Abatacept).
5. Development of new therapies has dramatically increased our ability to treat children with JIA, and hopefully induce remission in many children.
6. It is important for pediatric rheumatologists in turn to objectively assess patients, look at the core set criteria in these patients at set points in time, and guide therapy with the aim to achieve remission as per standard definitions.

Chapter 46.4
Large Vessel Vasculitis: Takayasu Arteritis

Anju Gupta

Takayasu arteritis is a chronic idiopathic granulomatous large vessel vasculitis. It typically involves elastic arteries, i.e., aorta and its major branches. It typically is a panarteritis involving all the three layers of vessel wall producing a typical pathology characterized by stenosis, occlusions, aneurysms and rarely rupture. Typical clinical features are ascribed to distal ischemia.

HISTORY

No other disease in humans has so much to owe to Japanese physicians as this disease. The first published description dates back to 1908 when a Japanese ophthalmologist, Mikito Takayasu, described *coronary anastomosis* in retinal vasculature in a 21 years old woman. Two more ophthalmologists namely Katsutomo Onishi and Tsurukichi Kagoshima also described similar findings and observed absence of radial pulsations in their patients. Yasuzo Shinmi used the term *Takayasu arteritis* for the first time in 1939.

First autopsy showing panarteritis of the aorta, and its major branches was reported by T Okabayashi in 1938. Later Kunio Oohta reexamined the same autopsy in more detail and described pulmonary artery involvement for the first time. He also attributed *coronary anastomosis* in retinal vasculature to ischemia of cerebrovascular circulation. Kentaro Shimizu and Keiji Sano described the triad of pulselessness, coronary anastomosis in retinal vasculature, and accentuated carotid sinus reflex in 1948. Even after so many years of initial description, we still do not know much about its etiology and pathogenesis.

EPIDEMIOLOGY

For the initial 40 years after first description, this disease was described only from Japan. However, later this disease has been described from all over the world though Asians seem to be more predisposed. The reported incidence is 2.6 per million of population per year. Usual age at onset is 10–40 years with 20–30% cases occurring in childhood. Females are 2–4 times more likely to get this disease.

ETIOPATHOGENESIS

Etiology of this disease is still unknown and pathogenesis predominantly involves cell-mediated immunity. This disease starts with involvement of vasa vasorum, which are vessels supplying arterial wall. An unknown stimulus causes expression of heat shock protein in aortic tissue which induces MHC class 1 chain related A (MICA) on vascular cells. The $\gamma\delta$ T cells and NK cells recognize MICA on vascular smooth muscle cells and release perforin, resulting in acute vascular inflammation. Pro-inflammatory cytokines increase the recruitment of mononuclear cells within the vascular wall. Th1 lymphocytes drive the occasional formation of giant cells through the production of interferon-γ, and activate macrophages with release of various growth factors resulting in increased neovascularization, smooth muscle migration and intimal proliferation.

PATHOLOGY

Pathologically, the disease can be seen in acute florid inflammatory phase or a healed fibrotic phase. In the acute phase, initial involvement occurs in vasa vasorum in adventitia. There is infiltration by lymphocytes and occasional giant cells in media followed by neovascularization and intimal thickening. In the chronic phase, there is fibrosis with destruction of elastic tissue. The lumen is narrowed in a patchy distribution, often affecting multiple areas. If disease progression is rapid, fibrosis can be inadequate with subsequent aneurysm formation.

CLINICAL FEATURES

Clinical features may vary from asymptomatic disease picked up due to impalpable pulses to catastrophic features like renovascular hypertension and cerebral ischemia. The clinical features occur usually due to distal ischemia. The most common presentation in childhood is renovascular hypertension occurring due to either renal artery involvement or suprarenal aortic involvement. Hypertension is usually severe and may or may not be associated with differential pulses depending on the site involved. Advanced stenosis in bilateral renal arteries could lead to renal dysfunction. Claudication is not a common symptom in childhood, probably because of inability to express this symptom. We have occasionally observed this complaint in adolescents with this disease. Bruits are common and could be heard at the site of arterial involvement. Impalpable pulses especially proximally in brachial, carotid or femoral arteries indicate proximal obstruction and this is an important sign of the disease. Carotidynia (tenderness on palpating carotid arteries) has been described, however is distinctly uncommon.

Organ-specific ischemic features may be seen like stroke, seizures in central nervous system, and visual disturbances in eye. Cardiac dysfunction is common in children and has been ascribed to both increased afterload and cardiomyopathy. Though mesenteric circulation is usually affected in types 3 and 4 diseases, mesenteric ischemia is distinctly uncommon because of extensive collateralization.

Pre-pulseless disease (before onset of stenosis) usually presents with nonspecific features like fever, malaise, night sweats, anorexia and weight loss. In this stage, there may not be any specific features and hence diagnosis is very difficult in this stage. Some authors have used PET scan in this stage to make a diagnosis however this modality is not well standardized for diagnosis yet.

CLASSIFICATION AND SUBTYPES

Table 1 provides the angiographic classification of Takayasu arteritis. There are certain regional differences in type of the disease. In Japan, types 1 and 2a are the most common variants, and hence the typical clinical features of absent pulses in upper limb (pulseless disease), and features of CNS and eye ischemia. Eye examination may show features of ischemic retinopathy and retinal microaneurysms. Hypertension will not be present in these variants.

In India, types 3 and 4 are the common variants; thus explaining an entirely different clinical presentation. These variants are not associated with so called *pulselessness* and features of CNS and eye ischemia. Instead, lower limb pulses would be feeble with significant hypertension in upper limbs. Cardiac decompensation is more frequent and CNS involvement occurs due to severe hypertension. Eye examination may show features of hypertensive retinopathy.

Table 1 Angiographic classification of Takayasu arteritis, Takayasu conference 1994

Type I	Branches from the aortic arch
Type IIa	Ascending aorta, aortic arch and its branches
Type IIb	Ascending aorta, aortic arch and its branches, thoracic descending aorta
Type III	Thoracic descending aorta, abdominal aorta, and/or renal arteries
Type IV	Abdominal aorta and/or renal arteries
Type V	Combined features of types IIb and IV

According to this classification system, involvement of the coronary or pulmonary arteries should be designated as C (+) or P (+), respectively.

DIAGNOSIS

Diagnosis in pulseless or stenotic phase is not difficult, once suspected. Most of the times errors are committed at the stage of history and examination itself, when one fails to take blood pressure or observe pulses in all four limbs. One must suspect this condition in the following settings:

- Hypertension
- Congestive heart failure
- Visual complaints
- Stroke/seizures/syncope

In all such children, one must observe pulses in all four limbs as well as carotids and take blood pressure and if the child is hypertensive, one must take blood pressure in all four limbs. This basic examination is enough to make one think of this disease in most settings.

Once this disease is suspected, the gold standard for diagnosis is angiography. Prior to going in for angiography, investigations like ultrasound to look for kidney size, Doppler to look for stenosis in abdominal aorta or renal arteries and echocardiography to look for cardiac dysfunction are useful. Unilateral renal artery stenosis may present with discrepancy in renal size, whereas bilateral stenosis may not show this discrepancy. Doppler of renal and carotid arteries is useful in picking up abnormal flow related to stenosis, however, it may be difficult to visualize aorta with this modality. Echocardiography may show evidence of cardiac dysfunction.

Conventional angiography or digital subtraction angiography are the gold standard for diagnosis **(Boxes 1 and 2)**. The vascular imaging shows intra-arterial disease-related damage like occlusion, stenosis (which is usually proximal and ostial), dilatation, and aneurysms **(Figs 1 and 2)**. Usually, there is contiguous involvement of arteries however skip lesions may be seen. What conventional angiography does not show is the status of vessel wall itself. Inflammatory disease activity in the vessel wall

BOX 1 1990 ACR criteria for classification of Takayasu arteritis

A diagnosis of Takayasu arteritis requires that at least 3 of the 6 criteria are met.

1. Age at disease onset < 40 years
2. Claudication of extremities
3. Decreased brachial artery pulse
4. Systolic blood pressure difference >10 mm Hg between arms
5. Bruit over subclavian arteries or aorta
6. Arteriogram abnormality (narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental)

BOX 2 EULAR/PRES classification criteria 2006 for Takayasu arteritis

Angiographic abnormalities plus
Presence of at least one of the following features:

- Decreased peripheral artery pulse(s) or claudication of extremities
- Blood pressure difference >10 mm Hg
- Bruits over the aorta or its major branches
- Hypertension (related to childhood normative data)

may be better seen with CT or MR angiography, however these modalities have still not become standard of care.

Of late, PET scan has been used to detect inflammation in arterial wall. It is based on the principle of excessive glucose metabolism by inflammatory cells. However, it is expensive, and is associated with a significant radiation dose. Moreover, this investigation really needs to prove itself both for diagnosis and monitoring before becoming the standard of care.

DIFFERENTIAL DIAGNOSIS

Coarctation of aorta is a common differential diagnosis of types 3 and 4 Takayasu arteritis and presents usually with hypertension in upper limbs, decreased pulses in lower limbs and radio-femoral delay. Hypertension would usually be chronic and hence associated with left ventricular hypertrophy. Collaterals are more common because of long duration of illness. Echocardiography and Doppler help in diagnosis. Angiography would show a discrete lesion in aorta in juxtaductal region and poststenotic dilatation.

Infectious aortitis has been described due to tuberculosis and syphilis. Syphilitic aortitis has not been described in children. Tubercular aortitis usually presents with aneurysms rather than stenosis which is more common in Takayasu arteritis.

IgG4 related aortitis has been recently described predominantly in adults. It is an arteritis involving both media and adventitia that may also be associated with systemic features of the disease. Again, aneurysms are the mode of presentation. It is a relatively new entity and till date, a predominantly pathologic diagnosis.

MANAGEMENT

Management aims at suppressing vessel wall inflammation and relieving distal ischemia. Steroids are the mainstay to suppress inflammation and can be given intravenously as pulse dose or orally. Most patients would need additional immunosuppression and various drugs like methotrexate, azathioprine and mycophenolate have been used. There is hardly any literature to support the use of one drug over other. As a routine, we use parenteral methotrexate as the first line drug primarily because of large experience, low cost and relatively few side-effects even when this drug is used for years. Clinical effect requires 8–12 weeks of weekly subcutaneous doses and meanwhile steroids are tapered to a low single daily dose. Other centers have used mycophenolate as the first line therapy along with steroids.

Some centers would recommend stronger immunosuppression with cyclophosphamide, in cases who present with Takayasu retinopathy, secondary hypertension, aortic regurgitation or aneurysm formation. These four complications have been shown to influence outcome. Duration of immunosuppression is variable usually for few years. As vessel wall histopathology is usually not feasible because of the nature of vessels involved and because there is a poor correlation of vessel wall inflammation with serological parameters, it is difficult to pinpoint when to stop immunosuppression. Most centers would continue it for 2–3 years if there have been no relapses of the disease.

Figure 1 Conventional angiography showing obstruction of thoracic aorta
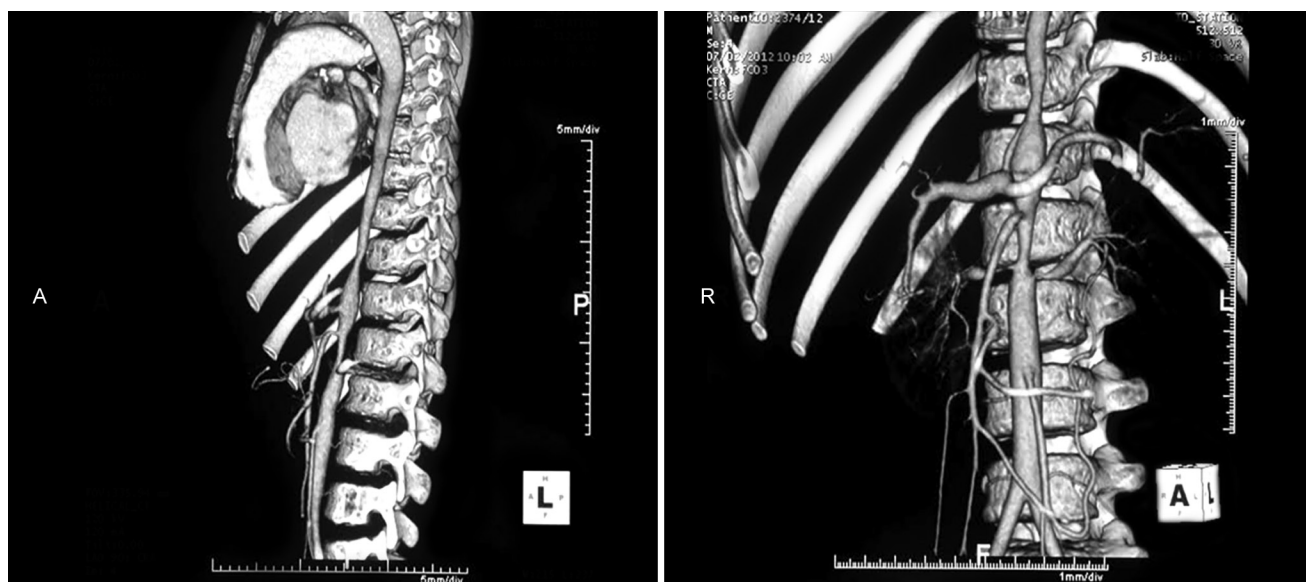
Figure 2 CT angiography showing obstruction of thoracic and abdominal aorta and its branches

Relief of distal ischemia requires percutaneous or surgical procedures in a vast majority of children with carotid, thoracic/abdominal aorta or renal artery involvement. Percutaneous procedures have been proven to be safe with not too different recurrence rates in comparison with surgical procedures. Hence, percutaneous procedures such as balloon angioplasty or stent graft placement are preferred for short-segment, critical arterial stenosis. Long-segment stenosis with extensive periarterial fibrosis or occlusion may require surgical bypass, however this also carries risk of anastomotic aneurysm and graft failure. As a general rule, if the condition of the patient permits, these procedures are avoided during acute inflammatory phase because of higher risk of dissection, anastomotic aneurysms and leak.

Besides these, most patients also need supportive therapy for control of hypertension and congestive heart failure. Renovascular hypertension is usually severe and needs multiple antihypertensive agents. One must remember not to give angiotensin converting enzyme inhibitors to control hypertension if the patients had bilateral renal artery stenosis or critical suprarenal aortic stenosis, as this may precipitate renal failure. One should also not control hypertension aggressively as this may precipitate frank ischemia distal to obstruction causing altered sensorium, stroke or seizures in patients with carotid involvement.

Antiplatelet agents are given as a routine to avoid thrombosis in stenosed vessels. Role of antitubercular therapy is controversial. Whereas most adult physicians would not recommend antitubercular therapy, we in our unit, give this treatment to all children who have a positive Mantoux test with Takayasu disease.

MONITORING

Monitoring includes monitoring for disease activity and drug adverse effects. Disease activity is difficult to define in this protracted disease associated with permanent damage. Symptoms

of worsening ischemia, physical examination for new signs like absence of pulse, bruit or blood pressure difference and inflammatory parameters like ESR and CRP are not sensitive to pick up active disease. Repeated angiography to look for involvement of new vessels or worsening of stenosis in a previously involved vessel is associated with a high radiation risk especially in chronic protracted diseases like this. MR angiography and FDG-PET scans may be useful to define activity of disease, however not proven beyond doubt. Though there has been an effort to make instruments to define disease activity like Disease Extent Index-Takayasu and Indian Takayasu Arteritis score (ITAS), these instruments are still not validated.

PROGNOSIS

It is a chronic disease with clinical relapses. In fact, it is very difficult to define remission because of paucity of serological biomarkers. A monophasic course is seen in about 20% patients. Most patients would keep on having relapses. Adult survival rates of 94–97% at 10–15 years have been achieved with immunosuppression and revascularization procedures. Higher mortality is seen however in children because of higher rate of congestive heart failure due both to hypertension and myocardial inflammation.

MORE ON THIS TOPIC

Arnaud L, Haroche J, Mathian A, et al. Pathogenesis of Takayasu's arteritis: A 2011 update. Autoimmun Rev. 2011;11:61-7.

Brunner J, Feldman BM, Tyrrell PN, et al. Takayasu arteritis in children and adolescents. Rheumatology. 2010;49:1806-14.

Direskeneli H, Aydın SZ, Merkel PA. Assessment of disease activity and progression in Takayasu'sarteritis. Clin Exp Rheumatol. 2011;29:S86-91.

Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol. 2002;55:481-6.

Keser G, Direskeneli H, Aksu K. Management of Takayasu arteritis: a systematic review. Rheumatology. 2013;October 4.

Numano F. The story of Takayasu arteritis. Rheumatology. 2002;41:103–6.

Ogino H, Matsuda H, Minatoya K, et al. Overview of late outcome of medical and surgical treatment for Takayasu arteritis. Circulation. 2008;118:2738-47.

Sharma S, Gupta A. Visceral artery interventions in Takayasu arteritis. SeminIntervent Radiol. 2009;26:233-44.

IN A NUTSHELL

1. Takayasu arteritis is a granulomatous large vessel arteritis of unknown etiology with stenosis or occlusion of aorta and/or its major branches. Aneurysms are less frequently seen.
2. Clinical features are related to distal ischemia and effects thereof:
   a. Renal ischemia can cause renovascular hypertension and renal dysfunction, if bilateral. Renovascular hypertension is usually severe and may cause cardiac, nervous system and renal decompensation. Cardiac decompensation due to severe hypertension as well as myocardial inflammation is common in children.
   b. Nervous system ischemia due to carotid involvement can cause seizures, syncope and stroke.
   c. Eye involvement due to ischemia can cause visual manifestations.
   d. Claudication is not a common complaint in children.
3. Diagnosis is not difficult if suspected. Conventional angiography is the gold standard for diagnosis.
4. Management is difficult and aimed at suppressing vessel wall inflammation and relieving distal ischemia. Inflammation is controlled by steroids and other steroid–sparing immunosuppressants. Relief of distal ischemia may need percutaneous or surgical procedures, which are usually done once inflammation subsides with immunosuppression.
5. Histopathology of vessel wall is usually not feasible except for the ones needing revascularization surgery. Short of histopathology, serologic markers do not accurately correlate with vessel wall inflammation.

Chapter 46.5
Medium Vessel Vasculitis: Kawasaki Disease and Polyarteritis Nodosa

Sikha Agarwal, Surjit Singh

Childhood vasculitis is a complex group of disorder with multisystem involvement. The diagnosis is often challenging as symptoms may be nonspecific and there are often no confirmatory laboratory parameters. The disease manifestations are affected by the site and size of the vessel involved. Medium vessel vasculitis encompasses two important disorders: Kawasaki disease and polyarteritis nodosa (PAN).

KAWASAKI DISEASE

Kawasaki disease (KD) is an acute, self-limiting multisystem vasculitic disorder involving the medium-sized arteries with a predilection for the coronary arteries. It was first described 47 years ago by Tomisaku Kawasaki. It is now the most common pediatric vasculitis, the most common cause of myocardial infarction in children, and the most common cause for acquired heart disease in children in Japan, North America and Europe. It is being increasingly reported from developing countries including India.

Epidemiology

Since Dr Kawasaki's initial report, KD has been identified throughout the world and in all races. The annual incidence rates are 239.6 per 100,000 children aged 0 to 4 years in 2010 in Japan. Following Japan, the second highest average annual incidence of KD is in South Korea. It has an incidence of 134.4 per 100,000 children less than 5 years of age in 2011. In Taiwan, the highest annual incidence of 66.24 per 100,000 children less than 5 years of age has been documented. There is paucity of data from developing countries. Some studies have shown that 24% of all vasculitic disorders are due to KD. According to some studies, KD has been found to outnumber the total number of cases of Henoch-Schönlein purpura (HSP). Based on extrapolation of our hospital data, an incidence of 4.54 per 100,000 children below 15 years of age has been computed for Chandigarh. KD is an illness of early childhood with maximum children below 5 years of age. The male:female ratio is 1.5:1 to 2:1; and there is a marked seasonality with maximum incidence in winters in temperate countries and summers in Asian countries.

Etiology

The etiology of KD is still an enigma. Many hypotheses are being postulated but so far none has been conclusively proven. A large global study for seasonality of KD demonstrated a statistically significant pattern with the sites located in the Northern hemisphere extra-tropics demonstrating a peak incidence in winter/spring, i.e., between January and March and a nadir between August and October. This suggests an environmental trigger for KD. In our institute as well, clustering of cases are seen, but with a different bimodal seasonality. Peak occurrence is in autumn and peak summer, i.e., in the month of October and May.

An infective etiology is suggested by the occurrence in a defined age group of children—infancy and young children. It is rarely seen at less than six months of age when protective maternal antibodies are present or in adults when the immune system is mature. Also the occurrence in epidemics and the clinical features such as fever, rash, and lymphadenopathy suggest an infective etiology. Another postulation is the involvement of super-antigen in the causation of KD. The clinical and immunological similarities between KD and the staphylococcal and streptococcal toxic shock syndromes suggest this possibility. A genetic association of the disease has also been considered. It is supported by the fact that there is an increased risk in siblings of children who have KD by 10-fold. It is two times more common in children of parents who themselves had KD in childhood. Incidence studies from Hawaii have shown an increased incidence in Asian and Pacific Islander children, especially Japanese children as compared to native Hawaiian children and hence reflect important racial and ethnic differences in genetic susceptibility to KD.

Pathology

Kawasaki disease predominantly involves medium-sized arteries with a predilection for the coronary arteries. Coronary involvement starts with necrotizing neutrophilic arteritis. This is followed by a subacute inflammatory vasculitis and stenosing proliferative myofibroblastic lesions. The vasculitic process in KD commences simultaneously with the onset, rapidly reaches an inflammatory peak, and then slowly remits and heals with cicatrization.

Clinical Features

Kawasaki disease remains a clinical diagnosis with no confirmatory laboratory test. The criteria for diagnosis of KD are given in **Box 1**. Fever more than 5 days along with any four of the five criteria is a pointer towards KD. It has also been suggested that in presence of coronary artery lesions, a diagnosis of KD can be considered even if there are less than four of the said criteria.

Fever is often high spiking, remittent, up to 39°C, and marginally responding to antipyretics. If untreated, it usually lasts for more than 11 days. After infusion of intravenous immunoglobulin, fever subsides within 48 hours. Bilateral conjuctival congestion, involving the bulbar conjunctiva but sparing the limbus is seen. It is usually painless and not associated with exudates or corneal ulceration. The oral mucosa is erythematous, with cracking/fissuring of the lips and erythema of the tongue (strawberry tongue).

The rash usually begins within the first week of illness. Rash can be nonspecific, urticarial, scarlatiniform, erythema-multiforme like lesions or scaling plaques. It is usually present on the trunk and the extremities with perineal accentuation. Presence of bullous and vesicular eruptions, however, is a pointer against KD. Erythema and induration of the palms and soles are often seen in the acute stage. In the subacute phase, within 2–3 weeks of onset of fever, desquamation of the fingers and toes are seen which is characteristic for the disease though not pathognomonic. It usually begins in the periungual region. In the convalescent phase, Beau's line (transverse ridged lines which start from the base of the nail and grow out) can be seen.

BOX 1 Classic clinical criteria of Kawasaki disease

- Fever persisting for at least 5 days
- Presence of at least 4 principal features
  – Extremity changes:
    - *Acute stage:* Erythema of palms and soles, edema of hands and feet
    - *Subacute stage:* Periungual peeling of fingers and toes
  – *Rashes:* Polymorphous
  – *Conjunctival congestion:* Bilateral bulbar conjunctiva without exudate
  – *Lips and oral cavity:* Lip cracking, erythema, strawberry tongue
  – *Cervical lymphadenopathy:* Usually unilateral, > 1.5 cms size
- Exclusion of other causes

Cervical lymphadenopathy, usually unilateral and confined to the anterior triangle may be present. The criteria are more than or equal to 1 lymph node which is greater than 1.5 cm in size. It is the least common of the classical features and is seen in only 50% of cases.

Like other vasculitis, involvement of the other systems in KD is common. The child may be irritable disproportionate to the degree of fever. It may be contributed by many factors such as urethritis/meatitis, aseptic meningitis, hydrops of the gall bladder, mild hepatitis, and arthritis. Another important finding that can be seen in an infant with KD is BCG scar reactivation. It is considered as one of the specific and early manifestation of KD. The mechanism is cross reactivity of T cells in KD patients between specific epitopes of mycobacterial and human heat shock protein. Patients with KD can present with cardiovascular compromise in view of the cardiac complications and can be mistaken to be due to systemic sepsis. There may be transient sensorineural hearing loss. Anterior uveitis has been seen in 66% of cases with KD presenting as redness and photophobia. Clinical examination may reveal tachycardia, hyperdynamic precordium with an innocent flow murmur. In the acute phase, there can be myocarditis with depressed myocardial contractility; pericarditis with a small pericardial effusion; or involvement of the valves—mitral regurgitation being the most common. Coronary artery abnormalities on echocardiography are usually seen after first week of illness. Patients less than 6 months and more than 5 years are at the highest risk of developing cardiac complications, in part due to the late diagnosis and delayed treatment.

Exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions, bullous/pustular/vesicular rashes, splenomegaly and laboratory investigations showing lymphocytosis are not suggestive of KD and an alternate diagnosis should be considered.

When untreated, KD usually progresses in three phases. The acute stage lasts 1–2 weeks and is characterized by fever and other acute signs of illness. The subacute stage over next 2 weeks is characterized by thrombocytosis, desquamation and cardiac involvement. The convalescent phase lasts up to 6–8 weeks till ESR and CRP normalize.

Laboratory Tests

There is no test which by itself is specific for KD. But like the clinical criteria, many laboratory features are typically found in KD. Even a complete blood count can give many clues to the diagnosis. Leukocytosis, predominantly neutrophilic is present during the acute stage of the disease. In presence of lymphocytosis, the diagnosis should be in doubt. Anemia, usually normocytic and normochromic is found. Thrombocytosis, which is said to be typical, however does not occur in first week of illness. There may be thrombocytopenia in the acute phase which has been shown to be a negative prognostic marker.

Acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are universally elevated. CRP may be a guide to the degree of inflammation in the subacute phase and following therapy with IVIg as well. ESR increases after IVIg infusion and hence, loses its value after IVIg infusion. Hypoalbuminemia is common.

The innumerable signs and symptoms of involvement of other organ systems can be depicted by laboratory tests as well. Sterile pyuria due to urethritis, elevation of liver transaminases indicating hepatitis and cerebrospinal fluid (CSF) mononuclear pleocytosis with normal glucose, protein and culture indicative of aseptic meningitis may be present. The lipid profile trends show marked alteration which tends to persist.

Two dimensional echocardiography forms the backbone for evaluating a child with KD. In acute phase, typical coronary aneurysms are usually not seen; but features of coronary arteritis such as perivascular brightness and lack of tapering of coronaries may be seen. Other features like decreased LV function, mitral regurgitation, and pericardial effusion may also be present. It is important to remember that a normal echocardiographic study does not negate the diagnosis of KD and in presence of classic criteria, the treatment should not be delayed.

Echocardiography should be done at the time of diagnosis and then 2–3 weeks later. If normal, it is repeated again after 6–8 weeks of onset of the illness. If any of the results are abnormal, more frequent follow-ups are warranted.

Incomplete Kawasaki Disease

A child with fever more than 5 days but only 2 or 3 instead of four of the classic clinical criteria is considered to have incomplete KD. These are a challenging subset of patients sometimes causing a huge diagnostic dilemma. They account for nearly 15–20% of cases in many case series. The supplementary laboratory criteria as described above along with echocardiograph findings are used to aid the diagnosis of incomplete KD.

Differential Diagnosis

Differential diagnosis includes toxic shock syndrome (staphylococcal and streptococcal), staphylococcal scalded skin syndrome, scarlet fever, and infections with adenovirus, measles, influenza etc. Resistant KD has to be differentiated from systemic onset juvenile idiopathic arthritis, PAN and malignancy (particularly lymphoma).

Treatment

The main aim of treatment is to reduce inflammation and prevent the coronary complications. Intravenous immunoglobulin is the mainstay of treatment. Many dose regimens have been followed, but the currently recommended regimen is the use of 2 g/kg in a single infusion started before 10 days of the illness. Meta-analysis of the randomized control trials comparing the efficacy of divided dose of IVIg versus a single infusion of 2 g/kg has shown therapeutic benefits of the later regimen in prevention of the coronary artery aneurysms. The infusion rapidly leads to the decline of fever and improvement of other clinical signs. Though it is being used for the past 30 years, the exact mechanism of action of IVIg is yet unknown. The other important component of the therapy is aspirin. It has anti-inflammatory and anti-platelet activity, though it has not been found to reduce the incidence of development of coronary artery aneurysms. It is started at a dose of 30–50 mg/kg/day along with IVIg therapy. Once the inflammatory parameters improve and the child becomes afebrile, this dose is reduced to 3–5 mg/kg/day for at least 6–8 weeks. If the echo at 6–8 weeks shows no evidence of coronary changes, then aspirin can safely be stopped. If the coronaries are abnormal, then aspirin may have to be continued indefinitely.

Tumor necrosis factor (TNF) antagonists are being increasingly used in KD. Tremoulet et al in 2014 have shown decrease in duration of fever and more reduction in inflammatory markers in patients who received IVIg along with Infliximab compared to those who received IVIg only, though there was no difference in the number of resistant KD. This suggests that anti TNF therapy has a beneficial effect on the inflammatory process in KD.

Complications

Cardiac complications are the most dreadful complications of KD; myocarditis and valvular involvement in acute phase and

coronary ectasia and aneurysms in subacute phase. Some patients even have presented in shock and been misdiagnosed as septic shock. Coronary involvement is seen in 20–25% patients who are not treated with IVIg. IVIg therapy reduces this risk to 3–5%. Giant coronary aneurysms, which are described as aneurysms more than 8 mm in size, are unlikely to regress and carry a risk of thrombosis, stenosis and rupture. Transient sensorineural hearing loss may occur in the acute phase but is rarely permanent.

Resistant Kawasaki Disease

Refractory/Resistant KD is defined as persistent or recrudescence of fever of more than 38°C at least 36 hours after completion of IVIg infusion. These patients have an increased risk of coronary artery aneurysms. Kobayashi et al had developed scoring system for prediction of immunoglobulin unresponsiveness in patients with KD. He included parameters as sodium 133 mmol/L; days of illness at the initial treatment 4 days; AST ≥ 100 IU/L; neutrophil ≥ 80%; CRP ≥ 10 mg/dL; age ≤ 12 months and platelet count ≤ 30 × 10^4/mm^3. A more aggressive anti-inflammatory treatment is warranted in these patients and it might reduce the occurrence of coronary artery aneurysms. Retreatment with a second dose of immunoglobulin is a common practice. Other options are use of steroid and TNF antagonists.

Long-term Management

Long-term management depends on the severity of cardiac damage. IVIg therapy has reduced the risk of coronary abnormalities from 25% to 3–5% and the incidence of giant aneurysm to less than 1%. In all patients with coronary artery abnormalities, aspirin is continued at a low dose of 3–5 mg/kg/day for long time. Cardiovascular risk assessment and counseling is done at an interval of 3–5 years in these patients. In patients with severe damage, close follow-up with myocardial perfusion scan and if required coronary angiography is done. Children with giant aneurysms require a second antiplatelet agent or the addition of anticoagulant—warfarin or low molecular weight heparin in addition to aspirin.

Assessment of risk factors like hypertension and hyperlipidemia should be done in all patients of KD irrespective of their cardiac status. Patients should be counseled to follow a healthy lifestyle and avoid modifiable cardiac risk factors.

POLYARTERITIS NODOSA

Polyarteritis nodosa is a necrotizing inflammation of medium sized arteries associated with the formation of aneurysmal nodules along the walls of the arteries. It has two different subgroups. One is the systemic form presenting with dermatologic, musculoskeletal, nervous, renal and gastrointestinal manifestations. The other is the cutaneous form with only skin involvement; the so-called benign cutaneous PAN. PAN is one of the most difficult conditions to diagnose in pediatric practice.

The classification criteria given by The European League against Rheumatism (EULAR) for childhood PAN are shown in **Box 2**. PAN occurs with similar frequency in both the sexes and the peak age of onset is 9–11 years.

The etiology of PAN is still not clearly known. Many viruses have been implicated; Hepatitis B being the most common. But this association is considered to be rare in pediatric population. Streptococcal infection is considered to be associated with the onset of Benign Cutaneous PAN.

Clinical Features

Nonspecific symptoms such as malaise, fever, weight loss, arthralgia and myalgia are present in majority of the patients **(Box 2)**. Cutaneous nodules are the most common skin

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BOX 2 Criteria for diagnosis of polyarteritis nodosa

- *Histopathology:* Evidence of necrotizing vasculitis in medium or small arteries

  Or
- Angiographic abnormality (aneurysm, stenosis or occlusion)

  PLUS
- Any 1 out of the following five
  1. Skin involvement
  2. Myalgia or muscle tenderness
  3. Hypertension
  4. Peripheral neuropathy
  5. Renal involvement (proteinuria, hematuria or impaired renal function)

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manifestation. These present as tender red nodules on the lower limbs. Livedo reticularis presents as a reticular cutaneous discoloration surrounding a pale central area, and is a characteristic finding in PAN. Cutaneous ulceration may occur. Neurological involvement occurs in about 50% patients and may be the presenting manifestation of the disease in some cases. Involvement of the peripheral nervous system is more common and can present as paresthesias or polyneuropathies. Kidneys may also be involved in systemic PAN causing hematuria and proteinuria due to infarction. But glomerulonephritis is rare as small vessel involvement is not a characteristic of PAN. Involvement of gastrointestinal tract in the form of abdominal angina has been reported and may have a grave outcome. In case of cutaneous PAN, periodic exacerbations and remissions have been described.

Laboratory Tests

Hemogram may reveal leukocytosis, anemia and thrombocytosis. Elevated ESR and CRP can be seen. Antineutrophil cytoplasmic antibodies (ANCA), seen in other necrotizing vasculitides, are characteristically absent. Angiographic findings like aneurysms, stenosis or occlusion on digital subtraction angiography are the hallmark of PAN and help in arriving at a diagnosis. As this is an invasive procedure, magnetic resonance (MR) or computerized tomography (CT) angiography have been used, though still are not gold standard. Increase in antistreptolysin O in the serum is seen in patients with cutaneous PAN. Skin biopsy in patients with cutaneous PAN shows necrotizing nongranulomatous vasculitis.

Treatment

Glucocorticoids form the mainstay of treatment for systemic PAN. Prednisolone is started at a dose of 1–2 mg/kg/day for 4–6 weeks and then tapered depending on the clinical response. Intravenous methylprednisolone is used in patients with severe disease. The most commonly used additional immunosuppressive agent is cyclophosphamide. It can be used as an oral therapy at a dose of 1–2 mg/kg/day for 2–4 months or intravenous pulse dose of 500–750 mg/m^2/month for 6 months. A higher cumulative dose has been shown to reduce the risk of relapse but with a possibility of increase in long-term side effects. Once remission is attained, maintenance dose of azathioprine is used for several months. Intravenous immunoglobulin has also been used in patients with severe PAN. Other drugs that have been used most recently are the biological agents, infliximab and rituximab. For cutaneous PAN, the mainstay is local supportive measures like leg elevation, avoidance of standing and NSAIDs. For mild recurrent or persistent disease, low dose steroids can be used.

Over the years, the outcome of systemic PAN has improved dramatically with the use of immunosuppressive agents. It still remains a life threatening disease in children and warrants early diagnosis and aggressive treatment.

IN A NUTSHELL

1. Kawasaki disease (KD) is the most common acute vasculitis of childhood.
2. Clinical features include fever, nonexudative conjunctivitis, cervical lymphadenopathy, skin and mucosal changes. It is important to remember that all these clinical features may not be present at a single point.
3. No laboratory investigation is diagnostic of KD in acute phase. Most features indicate inflammation like leukocytosis, high ESR, high CRP, hypoalbuminemia, transaminitis and sterile pyuria. Thrombocytosis, said to be so typical of this disease is not seen in first week of illness.
4. Periungual desquamation, so typical of KD, is also seen in subacute phase and hence does not help during the acute phase when IVIg therapy is most effective.
5. Intravenous immunoglobulin therapy is the mainstay of therapy with a clinical benefit of significant reduction in coronary abnormalities and should be given within first ten days of illness. Aspirin therapy acts as an adjunct anti-inflammatory agent in acute phase and an antiplatelet agent in convalescent phase.
6. Echocardiography in acute phase is often nonspecific and does not reveal typical coronary involvement.

MORE ON THIS TOPIC

Burns JC, Kushner HI, Bastian JF, et al. Kawasaki disease: A brief history. Pediatrics. 2000;106:E27.

Dillon MJ, Ozen S. Kawasaki disease in Cassidy JT, Petty RE. Eds Textbook of Pediatric Rheumatology, 6th ed. WB Saunders Company; 2011. p. 498-504.

Hernandez-Rodriguez J, Alba MA, Prieto-González S, Cid MC. Diagnosis and classification of polyarteritis nodosa. J Autoimmun. 2014;48-9:84-9.

Kawakami T. A review of pediatric vasculitis with a focus on juvenile polyarteritis nodosa. Am J Clin Dermatol. 2012;13:389-98.

Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315: 341-7.

Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics. 2004;114:1708-33.

Orenstein JM. Kawasaki Disease has so much to teach us! Ultrastruct Pathol. 2014;38:83-5.

Ozen S, Anton J, Arisoy N, et al. Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr. 2004;145:517-22.

Singh S, Kawasaki T. Kawasaki disease—an Indian perspective. Indian Pediatr. 2009;46:563-71.

Son MB, Newburger JW. Kawasaki disease. Pediatr Rev. 2013;34:151-62.

Chapter 46.6
Small Vessel Vasculitis: ANCA Associated Vasculitis and Henoch-Schönlein Purpura

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Vasculitis is a clinicopathological process characterized by inflammation and damage to blood vessels causing ischemia to the tissue supplied by it. It represents a heterogeneous group of clinical conditions having varied causes, but pathologically restricting to a few histological patterns of vascular inflammation. The symptomatology primarily depends on the site, type and size of the vessel involved which is used for classification of these disorders. Vasculitis and its consequences may be the primary or sole manifestation of a disease, alternatively may be a secondary component of primary disease. It may be confined to a single organ, i.e., skin, or it may simultaneously involve several other organ systems.

CLASSIFICATION AND NOMENCLATURE

The European League of Association for Rheumatology (EULAR) along with the Pediatric Rheumatology European Society (EULAR-PRES) proposed a classification of childhood vasculitides. The scheme uses the vessel size for classification purpose. The aorta and its main branches are termed as the large vessels; the first branches of the aorta, such as the renal, mesenteric, coronary vessels are categorized as medium-sized. Small vessel vasculitides is defined as vasculitis that affects vessels smaller than arteries, such as arterioles, capillaries and venules. The latter has further been sub-divided on the basis of histopathological findings into granulomatous and nongranulomatous varieties **(Box 1)**.

EPIDEMIOLOGY

The first reported case of necrotizing arteritis by Kussmaul and Maier in 1866 was described as *periarteritis nodosa* and it finally evolved into a more pathologically correct name polyarteritis nodosa (PAN). Till the 1950s, most patients presenting with necrotizing arteritis were diagnosed as PAN, when investigators realized that there were a number of clinically and pathologically distinct forms of arteritis and where most of the involved vessels were smaller than arteries. Zeek et al termed this small-vessel involvement as *hypersensitivity angiitis*, where as Davson et al, and Godman and Churg referred to it as microscopic form of periarteritis. It was during this time that two variants of vasculitides with associated necrotizing granulomatous inflammation had been reported—Wegener's granulomatosis (WG) and Churg-Strauss syndrome (CSS). Purpura was the first manifestation

of vasculitis in vessels smaller than arteries to be extensively investigated. In 1808, Willian clearly distinguished purpura caused by systemic febrile infections from noninfectious purpura. Over the next century, Schönlein, Henoch, Osler and others described a broad spectrum of signs and symptoms that were associated with purpura and thus with small vessel vasculitis. The advent of immunofluorescence microscopy led to discovery of cryoglobulins and IgA deposits. The concept of immune-complex pathogenesis for some forms of small-vessel vasculitis emerged, but the absence or 'paucity' of the latter in many important categories, including WG, CSS, microscopic polyangiitis (MPA) was unsettling. This is again where the discovery of antineutrophil cytoplasmic antibodies contributed to the better understanding of small-vessel diseases.

ETIOPATHOGENESIS

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

These were first detected by Davies et al in 1982 as antibodies reacting to neutrophil cytoplasm in patients of pauci-immune necrotizing glomerulonephritis and small-vessel vasculitis. There are two major categories of ANCA based on different targets for these antibodies. Serum antibodies binding to indicator neutrophils producing a diffuse granular cytoplasmic staining pattern on immunofluorescence microscopy is referred to as cytoplasmic ANCA (c-ANCA). The target antigen is proteinase-3, a neutral serine protein found in the neutrophil azurophilic granules. Around 90% patients of active WG have detectable antibodies to proteinase-3. A more localized perinuclear or nuclear staining pattern is seen with perinuclear ANCA (p-ANCA). The target antigen for p-ANCAs are varied, the most common being enzyme myeloperoxidase. These are found in variable percentage of patients of MPA, CSS, crescentic glomerulonephritis, Goodpasture syndrome and WG.

The role of ANCAs in the pathogenesis is difficult to define but this understanding is required for application of more specific therapeutic agents. It is proposed that these auto-antibodies activate cytokine primed neutrophils and monocytes which then express ANCA antigens on the cell surface. Neutrophils then respond by adhering to cytokine-activated endothelial cells, generating a respiratory burst, releasing proteolytic granule contents and secreting pro-inflammatory cytokines. There is also interference with normal process of resolution of inflammation and dysregulated neutrophil apoptosis allowing progression to secondary necrosis.

Approximately 10% patients of typical WG or MPA have negative assays for ANCA. Thus ANCA negativity does not completely rule out these diseases.

ANCA-ASSOCIATED VASCULITIS

Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA) are three distinct forms of ANCA-associated vasculitis. They share certain common features: the most characteristic being the histopathologic finding of focal necrotizing lesions, which may affect different vessels and organs. In the lungs, capillaritis can cause alveolar hemorrhage. Involvement of the glomeruli of kidneys presents with crescentic glomerulonephritis and involvement of dermal vessels can cause purpuric rash or vasculitic ulceration, subcutaneous edema, etc. **(Fig. 1)**. WG and CSS have the additional common feature of granulomatous lesions on biopsy. All these diseases have unique distinction of paucity of immune-complex deposition **(Box 2)**.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a necrotizing, granulomatous vasculitis predominantly involving the small vessels of the upper

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BOX 1 EULAR/PReS classification of childhood vasculitis (small vessels)

Predominantly small-sized vessel vasculitis
A. *Granulomatous*
   • Wegener's granulomatosis
   • Churg-Strauss syndrome
B. *Nongranulomatous*
   • Microscopic polyangiitis
   • Henoch-Schönlein purpura
   • Isolated cutaneous leukocytoclastic vasculitis
   • Hypocomplementic urticarial vasculitis

Figure 1 Urticarial rash and subcutaneous edema seen in hypersensitivity vasculitis

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BOX 2 Etiopathological categories of small vessels vasculitis

Small-vessel vasculitis
- ANCA-associated small-vessel vasculitis
    Microscopic polyangiitis
    Wegener's granulomatosis
    Churg–Strauss syndrome
    Drug-induced ANCA-associated vasculitis
- Immune-complex small-vessel vasculitis
    Henoch–Schönlein purpura
    Cryoglobulinemic vasculitis
    Lupus vasculitis
    Rheumatoid vasculitis
    Sjögren's syndrome vasculitis
    Hypocomplementemic urticarial vasculitis
    Behçet's disease
    Serum-sickness vasculitis
    Drug-induced immune-complex vasculitis
    Infection-induced immune-complex vasculitis

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and lower respiratory tract and kidney. Other organs may also be involved, as also other vessels like the medium-sized arteries. Most cases occur in adults, but this may be seen by pediatric rheumatologists with a mean age at diagnosis of 14 years. There is a female predominance and pediatric WG is prevalent in the white population.

Clinical Features

The triad of upper and lower respiratory tract inflammation and renal disease is the characteristic of WG. The common features are:
1. *Constitutional symptoms:* Fever, malaise, weight loss, fatigue
2. *Pulmonary (80%):* Cough, hemoptysis, dyspnea, pulmonary hemorrhage
3. *Ear, nose, throat (80%):* Rhinorrhea, epistaxis, sinusitis, otitis media, collapse of nasal bridge, tracheal stenosis
4. *Renal (75%):* Hematuria, proteinuria, red cell casts, deterioration of renal function with end-stage renal disease
5. *Skin:* Papules, vesicles, palpable purpura, ulcers, subcutaneous nodules
6. *Others:* Ocular abnormalities (episcleritis, uveitis, proptosis, optic nerve ischemia), Peripheral nervous system (mononeuritis multiplex), Heart (pericarditis, coronary vasculitis, myocardial ischemia), GI (ischemia and hemorrhage).

Diagnosis

The classification criteria, ACR criteria, which require 2 out of 4 described features (nasal/oral inflammation, abnormal chest radiograph, abnormal urinalysis, granulomatous inflammation on biopsy) are mostly devised for the adults. The EULAR/PReS classification **(Table 1)** is modified to suit the pediatric population. It takes in account the features which are more frequent and characteristic for children like the subglottic stenosis. It expands the laboratory and imaging findings and also includes the presence of ANCA antibodies.

Investigations

Following features may be present: normocytic normochromic anemia, leukocytosis, thrombocytosis, elevated ESR/CRP, abnormal urinalysis: hematuria, proteinuria, RBC casts; and elevated urea/creatinine. Serology may reveal antinuclear antibody of unknown specificity (20–36%), rheumatoid factor (50%), antiphospholipid antibodies (22%), increased immunoglobulins, cANCA (86%)—anti-PR3 (68%), or ELISA anti-MPO (14%). Histopathology reveals granulomatous vasculitis involving small arteries and veins in different organs mostly upper and lower respiratory tract. Kidneys initially show glomerular thrombosis, but most reported features have extracapilllary proliferation either or associated with fibrinoid necrosis and crescent formation, found in a focal segmental pattern. This progresses to necrotizing glomerulonephritis and glomerular sclerosis. Immunofluorescence microscopy does not detect immune-complex deposition—the pauci-immune pattern.

Chest radiography is abnormal in 41% of children with WG in the form of nodules and fixed infiltrates. High resolution CT is more effective in detecting characteristic changes such as small nodules, linear opacities, focal low attenuation infiltrates and fluffy centrilobular and perivascular densities. Sinus radiographs and CT are also diagnostic.

Differentiation from other types of small vessels vasculitis is listed in **Table 2**.

Microscopic Polyangiitis

This is a small vessel necrotizing vasculitis with clinical features similar to WG with mostly renal and pulmonary involvement. It was initially considered to be a subset of PAN but later came to be recognized as a separate disease entity characterized by necrotizing vasculitis, with few or no immune deposits and predominantly

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Table 1 Comparison of the ACR10 and proposed EULAR/PReS criteria for classification for Wegener's granulomatosis (WG)

ACR	EULAR/PReS
A patient is said to have WG when two of the following four criteria are present:	A patient is said to have WG when three of the following six criteria are present:
1. Nasal or oral inflammation	1. Nasal, oral inflammation or sinus inflammation
2. Abnormal chest radiograph	2. Abnormal chest radiograph or chest CT scan
3. Abnormal urinalysis	3. Abnormal urinalysis including significant proteinuria
4. Granulomatous inflammation on biopsy	4. Granulomatous inflammation on biopsy or necrotizing pauci-immune GN on biopsy
	5. Subglottic, tracheal, or endobronchial stenosis
	6. PR3 ANCA or c-ANCA staining

Table 2 Differential diagnostic features of several forms of small-vessel vasculitis

Features	HSP	Cryoglobuline-mic vasculitis	MPA	WG	CSS
Signs and symptoms of small-vessel vasculitis	+	+	+	+	+
IgA-immune deposits	+	-	-	-	-
Cryoglobulins	-	+	-	-	-
ANCA in blood	-	-	+	+	+
Necrotizing granulomas	-	-	-	+	+
Asthma and eosinophilia	-	-	-	-	+

Abbreviations: HSP, Henoch-Schönlein purpura; MPA, microscopic polyangiitis; WG, Wegener's granulomatosis; CSS, Churg-Strauss syndrome

Table 3 European Vasculitis Study (EUVAS) categorization of ANCA-associated vasculitides

Category	Definition
Localized	Upper and lower tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalized	Renal or other organ threatening disease, serum creatinine < 500 µmol/L
Severe	Renal or other vital organ failure, serum creatinine > 500 µmol/L
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

affecting small vessels. Necrotizing glomerulonephritis and pulmonary capillaritis are common. Among the few reported cases in pediatric population, the mean age of onset is 9–12 years with no gender predilection. Around 75% of the patients have p-ANCA specificity for MPO. The presence of ANCA and size of vessel involved differentiate it from PAN. The absence of granulomatous inflammation in microscopic polyangiitis distinguishes this small vessel disease from WG. Upper airway disease and pulmonary nodules are also not typical of MPA when compared to WG.

Churg-Strauss Syndrome (CSS)

Churg-Strauss syndrome is characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation and vasculitis of multiple organ systems. It is also termed as allergic granulomatosis and angiitis. Following clinical features are described:

- *Pulmonary*: Severe asthmatic attacks and pulmonary infiltrates
- *Peripheral neuropathy*: Mononeuritis multiplex, polyneuropathy
- *Cardiac involvement*: Cardiomyopathy
- *Allergic manifestations*: Chronic allergic rhinitis, nasal polyposis
- *Skin*: Purpura, subcutaneous edema, cutaneous nodules
- *Renal*: Mild and rarely progressive
- *Laboratory finding*: Eosinophilia with absolute eosinophil count > 1000 cells/microliter (or 10% or more of total leukocytes), elevated ESR, serum IgE, fibrinogen and alpha-2 globulin levels. Circulating ANCA is mostly anti-MPO, found in 48% of the patients
- *Histopathology*: Necrotizing vasculitis of small and medium sized arteries, capillaries, veins and venules. The characteristic feature is granulomatous reaction with infiltration of tissue by eosinophils.

Management of ANCA-associated Vasculitis

A major breakthrough occurred with the use of cyclophosphamide and high dose corticosteroids, first by Hoffman et al, and Fanci et al in 1970. As control of disease can be done in almost 80–90% of the patients, this drug regimen is now being viewed as the gold standard. Emerging medical therapy has led to the conversion of this acutely fatal disease into a chronic relapsing disorder with accumulation of treatment-related morbidities. Thus, treatment must be advised considering the stage and severity of disease so as to balance the risk-benefit ratio. The EULAR clearly recommends that patients with ANCA-associated vasculitis be categorized according to different levels of disease severity **(Table 3)**.

Early recognition of disease is essential on the basis of characteristic clinical markers and treatment is to be initiated promptly to reduce permanent scarring. The treatment discussed here applies to ANCA-associated vasculitides with prototype being WG.

Induction Therapy
The initial therapy requires high dose cyclophosphamide and corticosteroids. Adjustment of cyclophosphamide is to be done according to age, renal function and prevailing WBC count. It is usually continued for 3 months. Often pulse cyclophosphamide is used with less toxicity. It is potent inducer of remission, but with a higher relapse rate.

Maintenance Therapy
The maintenance therapy is to be balanced according to risk of disease relapse which occurs in 25–50% over 3–5 years. Azathioprine is as effective as cyclophosphamide in maintaining remission. WG is more likely to relapse than MPA. Weekly methotrexate is used in induction/remission of WG without threatened vital organ function. The drug is contraindicated in serum creatinine level of more than 2 mg/dL. The other drugs that can be used are mycophenolate mofetil (immunosuppressant with high lymphocyte specificity) or cyclosporin.

Cotrimoxazole Prophylaxis
This should be given in all patients with WG as staphylococcal colonization of the upper airway has been shown to increase risk of disease relapse.

Prognosis
The prognosis of untreated ANCA-associated vasculitides is poor with 90% of patients dying within 2 years usually due to respiratory failure. The most important indicators of prognosis are pulmonary hemorrhage and severity of renal failure at diagnosis. Patients with fulminant disease require intensification of induction therapy in the form methylprednisolone and plasma exchange.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein Purpura (HSP) is one of the common vasculitis in children. It is a multisystem, small-vessel, leukocytoclastic vasculitis.

Epidemiology
HSP is predominantly a childhood vasculitis, rarely reported in adults. Worldwide, the highest incidence is in the Asian population. It is often a self-limiting condition and hence exact incidence is not known and probably under reported. It is usually seen between the ages of 3 and 15 years and has a male preponderance. There is a seasonal trend in the distribution with a noticeable peak observed

in the months of October and November. Western data also report seasonal variation with most cases occurring in winter.

Etiology

HSP etiology is still not well established but is associated with infections, medications and vaccination. The infections implicated as a potential trigger are rubella, rubeola, parvovirus B-19, hepatitis A and B virus, and adenovirus.

Pathogenesis

HSP is an IgA-mediated dysregulated immune response to antigen as suggested by the deposition of immunoglobulin A (IgA). This association may explain the predilection of skin lesions for the lower extremities and buttocks in ambulatory children and sacrum along with buttocks and ears in infants as gravity causes immune complexes to deposit and incite inflammation in dependent areas. Vasculitis leads to extravasation of blood into the interstitial spaces resulting in edema and hemorrhage. This may involve multiple systems including skin, joints, gastrointestinal tract and kidney.

In the acute phase, serum levels of IgA anticardiolipin antibodies were elevated in a study by Yang and colleagues. Formation of circulating immune complexes and their mesangial deposition, resulting in renal injury could be due to recognition of galactose-deficient IgA_1 by antiglycan antibodies. Progression of renal injury has also been associated with renal expression of alpha-smooth muscle actin (α-SMA).

Rapid decline in factor XIII has been documented in patients with severe abdominal involvement. This decline is seen before the appearance of rash; hence it may be useful as a diagnostic marker in patients with abdominal symptoms.

Genetic predisposition is complex and polygenic in nature. HLA A1, B49, and B50 antigens were associated with decreased risk for HSP in children, whereas HLA A2, A11, and B35 antigens were associated with a significantly increased risk in a Turkish study by Peru and colleagues.

Pathology

The pathognomonic lesion for HSP is leukocytoclastic vasculitis and is seen in the dermal capillaries and postcapillary venules in the skin. Deposition of IgA (principally IgA_1) is also characteristic. Leukocytoclasis implicates the breakdown of white blood cells in lesional tissue, especially the nuclear debris ("nuclear dust"). Biopsy may stain negative for IgA, if obtained from the middle of a lesion, due to the presence of proteolytic enzymes.

In the renal system, the spectrum of glomerulonephritis ranges from focal and segmental lesions to severe crescentic disease. The characteristic lesion is an endocapillary proliferative glomerulonephritis with increase in endothelial and mesangial cells. All gradations of severity may be present in the same biopsy specimen. Immunoglobulin, principally IgA is seen in most involved glomeruli by fluorescence microscopy. Electron microscopy has demonstrated dense deposits in the mesangium and occasionally in the subendothelial and paramesangial regions.

Clinical Features

HSP is a clinical diagnosis and when in doubt, a tissue biopsy may be helpful. It is diagnosed by a classic tetrad of nonthrombocytopenic palpable purpura, articular, gastrointestinal and renal involvement **(Table 4)**. Skin involvement is the most common presentation. The onset is acute but symptoms may appear sequentially resulting in delay in diagnosis.

Cutaneous lesions, usually symmetric, begin insidiously as maculopapular eruptions which become palpable and purpuric. Gravity dependent areas especially lower extremities and buttocks favor the localization of rash **(Fig. 2)**. There may be an abundance of rash at the pressure points especially on the extensor aspect of the knees in crawling infants. The eruptions fade leaving a brownish color that may persist for weeks. Vesicles, erythema multiforme-like lesions, and hemorrhagic bullae may also be seen, though rare in children when compared to adults. Infants may develop marked

Figure 2 Purpuric rash on the lower extremities with ankle arthritis and edema of feet

Table 4 2010 classification criteria for Henoch-Schönlein purpura (EULAR/PReS)

Criterion	Definition	Sensitivity	Specificity
Purpura (mandatory)	Purpura (palpable, in crops) and or petechiae, with lower limb predominance,[*] not related to thrombocytopenia	89%	86%
And at least 1 out of 4 of the following			
Abdominal pain	Diffuse, acute, colicky pain. May include intussusception and gastrointestinal bleeding	61%	64%
Histopathology	Leukocytoclastic vasculitis with predominant IgA deposit; or proliferative glomerulonephritis with predominant IgA deposit	93%	89%
Arthritis or arthralgias	*Arthritis:* Acute joint swelling or pain with limitation on motion *Arthralgia:* Acute joint pain without joint swelling or limitation on motion	78%	42%
Renal involvement	Proteinuria > 0.3 g/24 hours; spot urine albumin to creatinine ratio > 30 mmol/mg Or Hematuria, red cell casts. Urine sediment showing > 5 red cells per high power field or red cell casts ≥ 2+ on dipstick	33%	70%

*If purpura with atypical distribution, demonstration of IgA deposit on biopsy is required.
Source: Adapted from Ozen S. The EULAR/PRINTO/PReS criteria for Henoch-Schönlein purpura. Ann Rheum Dis. 2010;5:798-806.

edema of face, scalp and extremities and have lesions on the face and ears. This is probably due to larger surface area of the head and face and proportionately higher blood supply. Involvement of the external genitalia is more commonly seen in boys when compared to men and include painless scrotal edema, purpura, acute onset edema of the glans penis or prepuce and acute testicular pain mimicking torsion.

Gastrointestinal manifestations are seen usually within a few days after the onset of rash and are due to vasculitis involving the splanchnic circulation. Abdominal pain is the predominant symptom. Other symptoms are nausea, vomiting, hematemesis, hematochezia and melena. Rare manifestations like massive gastrointestinal bleeding, intussusception (ileoileal), intestinal perforation, hemorrhagic ascites, pancreatitis, acute acalculous cholecystitis, and biliary cirrhosis are reported.

Renal abnormalities usually follow the onset of typical rash within three months. The manifestations range from microscopic hematuria and mild proteinuria to nephrotic syndrome, acute nephritic syndrome, hypertension, or renal failure.

Arthralgia or *arthritis* involving only a few joints occurs in up to 80% of children. The joint involvement is nonmigratory, nondestructive, symmetrical polyarthralgias/polyarthritis. The knee and ankle joints are most often involved. Joint disease is more common in adults. Resolution occurs within a few days. Occasionally, arthritis may precede the rash and delay diagnosis. Major clinical features of HSP in Indian children are summarized in **Table 5**.

Differential Diagnosis

Immune thrombocytopenic purpura, acute poststreptococcal glomerulonephritis, septicemia, disseminated intravascular coagulation, hemolytic-uremic syndrome, leukemia, SLE and other types of vasculitis are to be considered in the differential diagnosis. Common causes of an acute surgical abdomen with abdominal pain and gastrointestinal tract bleeding must be considered in the differentials. If there is a tender abdominal mass, intussusception can be considered and abdominal tenderness with an elevated serum amylase level may suggest acute pancreatitis. Diagnosis may be particularly challenging if the rash follows the onset of the abdominal symptoms.

Infantile acute hemorrhagic edema (Finkelstein-Seidlmayer syndrome) is usually seen in children below 2 years of age. The etiology could be preceding infection, immunization, and drugs however unlike HSP, IgA has limited role. Activation of a classical complement pathway could be one of the pathogenic mechanisms. It is characterized by acute onset of fever, purpura, ecchymoses, and inflammatory edema of the, ears, face and limbs. Visceral involvement is rare. There may be recurrent attacks. The biopsy shows leukocytoclastic vasculitis with occasional demonstration of perivascular IgA deposition.

Table 5 Major clinical manifestations of Henoch-Schönlein purpura: Indian Data

Clinical feature	Sarkar et al. n = 90	Kumar et al. n = 45	Bagai et al. n = 36	Grover et al. n = 30	Bagga et al. n = 47
Purpura (%)		100	100	100	95.7
Gastrointestinal (%)	7.7	78	58.3	80	63.8
Joint pain (%)		60	72.2	86.7	46.8
Renal (%)	10	31	47.2	30	51.1

Source: Adapted from: Kamath N, Rao S. Henoch–Schönlein purpura: An update. Indian J Rheumatol, 2012;7:92-8.

Investigations

HSP, as the other vasculitides, is a clinical diagnosis. Hemogram may show a normal or elevated platelet count. Leukocytosis with a left shift is seen. Normochromic anemia is often related to gastrointestinal blood loss, confirmed by a positive stool guaiac examination in children with abdominal symptoms. Rheumatoid factor, antinuclear antibody and antineutrophilic cytoplasmic antibodies are not of any significance. Urinary abnormalities demonstrate a direct correlation with the severity of the renal proliferative changes. Proteinuria may be severe enough to result in hypoalbuminemia.

C1q, C3, and C4 are usually normal in HSP. There is activation of the alternative complement pathway during the acute illness. This is confirmed by the presence of C3d, low levels of total hemolytic complement, and decreased concentrations of properdin and factor B in the serum.

Plain radiographs may show dilated bowel loops in children with abdominal symptoms. Ultrasound of the abdomen can demonstrate specific gastrointestinal abnormalities in children with abdominal complaints and confirm testicular torsion. Magnetic resonance imaging and magnetic resonance angiography can be done if symptoms and signs suggest cerebral vasculitis. Punch biopsy of a cutaneous lesion may confirm diagnosis of difficult cases by demonstrating a leukocytoclastic vasculitis characterized by deposition of IgA and C3 **(Fig. 3)**.

A renal biopsy is indicated in cases of persistent or significant renal manifestations. Indications for diagnostic renal biopsy are oliguria, hypertension, raised creatinine, nephritic/nephrotic presentation, persistent proteinuria (not declining) after 4 weeks and heavy proteinuria (Ua: Ucr persistently >100 mg/mmol) on an early morning urine sample at 4 weeks.

Treatment

The active, acute phase of HSP resolves spontaneously in most children and the primary goal of the pediatrician is to reassure the parents about benign nature of the disease and provide symptomatic treatment. The patient should be followed up for complications which usually occur within a month of initial presentation. Painful soft tissue edema and joint pain usually respond to acetaminophen or nonsteroidal anti-inflammatory drugs. Prednisone at 1–2 mg/kg per day for two weeks and
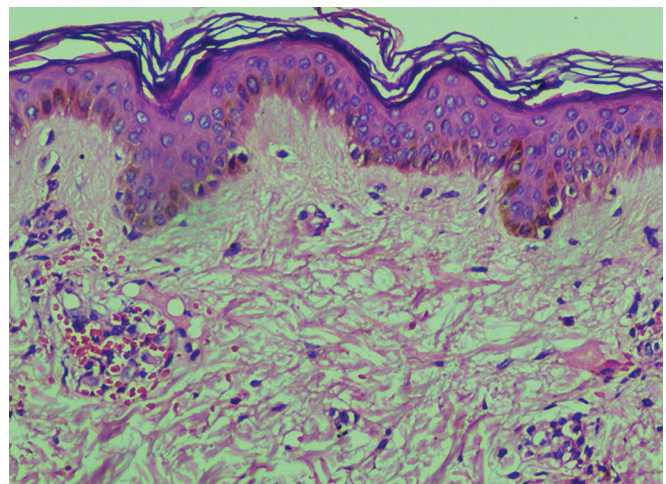
Figure 3 Photomicrograph of skin biopsy showing leukocytoclastic vasculitis
(*Source:* Dr Ramadas Nayak, Professor Pathology, Kasturba Medical College, Mangaluru).

tapered over next two weeks, may hasten their resolution. Anti-inflammatory agents should be avoided in children with extensive renal involvement. Corticosteroids can relieve abdominal pain within 24 hours without serious complications. Altugan and coworkers analyzed all cases with severe renal involvement, who were biopsied and treated as assigned (Class II: oral steroids, Class III (with crescentic nephritis): additional oral cyclophosphamide 2 mg/kg/day for 12 weeks, and Classes IV and V: azathioprine for 9 months following the treatment for Class III). Angiotensin converting enzyme (ACE) inhibitors were prescribed in all classes irrespective of their blood pressure values. Eighteen patients with severe HSP nephritis, defined as decreased renal function and/or heavy proteinuria, were evaluated. Seven of these had impaired renal function with GFR below 75 mL/min/1.73 m^2 at presentation. With the above treatment protocol, all patients had normal GFR at the end of four years of follow-up. Proteinuria was absent in all the patients and 8 had microscopic hematuria. This preliminary study suggested a stepwise treatment based on the renal histology. The favorable results with complete disappearance of proteins in the urine and normal renal function justified the use of immunosuppressive protocol with ACE inhibition. Prophylactic therapy with corticosteroids has no role in the prevention of the onset of HSPN. Renal transplantation has been successful in some children with renal failure.

Course of the Disease and Prognosis

HSP runs its entire course in most children within four to six weeks. Younger children usually have a shorter course with fewer complications and recurrences. Each recurrence is usually similar but briefer and milder. Exacerbations can be spontaneous or may coincide with recurrent respiratory tract infections. There is no correlation between the severity of the cutaneous leukocytoclastic vasculitis and visceral involvement.

Prognosis is excellent in most cases. Significant morbidity or mortality is documented with gastrointestinal tract lesions in the short-term and renal disease in the long-term. Renal disease within the first 6 months after onset or the occurrence of numerous exacerbations associated with nephropathy suggest a poor prognosis for renal function. Other poor prognostic factors are: severe purpuric lesions or renal failure at onset; hypertension; cardiac tamponade; reduced factor XIII activity and an increased number of glomeruli with crescents; macrophage infiltration and tubulointerstitial disease in renal biopsy. Presence of nephrotic or nephritic syndrome at onset is associated with the worst outcome. HSP contributes to less than 1% of children with renal failure from all causes. Children with clinical nephritis should be followed up for at least 5 years. The Alder Hey HSP Monitoring Pathway was developed for the screening of renal outcome in HSP. They followed up a cohort of 102 patients for five years. Normal urine analysis on day 7 had a 97% (Confidence interval 90–99%) negative predictive value in predicting a normal renal outcome. A six-month monitoring period for all patients presenting with HSP was devised according to the urine findings on day 7. Close monitoring was recommended for those at higher risk of developing nephritis.

IN A NUTSHELL

1. Vasculitis and its consequences may be the primary or sole manifestation of a disease or alternatively may be a secondary component of primary disease.
2. Small vessel vasculitis is defined as vasculitis that affects vessels smaller than arteries, such as arterioles, capillaries and venules. The latter has further been sub-divided on the basis of histopathological findings into granulomatous and non-granulomatous varieties.
3. Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS) and Microscopic polyangiitis (MPA) are three distinct forms of ANCA-associated vasculitis. They are far less common than HSP. They share certain common features: the most characteristic being the histopathologic finding of focal necrotizing lesions. The initial therapy requires high dose cyclophosphamide, methylprednisolone, corticosteroids, etc., followed by maintenance immunosuppressive therapy as per titration of disease activity along with cotrimoxazole prophylaxis.
4. HSP is one of the most common acute vasculitis of childhood and is characterized by leukocytoclastic vasculitis with deposition of IgA (principally IgA$_1$). Palpable purpura is the characteristic skin manifestation. Gastrointestinal complications are the most dreaded complications in acute phase. Usually it is a self-limited disease, however carries a risk of renal involvement in a minority of patients. Treatment is symptomatic in mild cases; steroids and immunosuppressive agents are indicated in severe cases. Patients must be followed up for at least 6 months for potential nephritis and its complications and for 5 years if nephritis is documented.

MORE ON THIS TOPIC

Altugan FS, Ozen S, Aktay-Ayaz N, et al. Treatment of severe Henoch-Schönlein nephritis: justifying more immunosuppression. Turk J Pediatr. 2009;51:551-5.

Chartapisak W, Opastiraku S, Willis NS, et al. Prevention and treatment of renal disease in Henoch-Schönlein purpura: a systematic review. Arch Dis Child. 2009;94:132-7.

Jennette JC, Falk RJ. Small-vessel vasculities. N Engl J Med. 1997;337:1512-23.

Kamesh L, Harper L, Savage CO. ANCA-Positive vasculitis. J Am Soc Nephrol. 2002;13:1953-60.

Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;5:798-806.

Ozen S, Ruperto N, Dillon M, et al. EULAR/PReS endorsed consensus criterion for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936-41.

Singh S, Aulakh R. Kawasaki disease and Henoch-Schönlein purpura: changing trends at a tertiary care hospital in north India (1993-2008). Rheumatol Int. 2010;30:771-4.

van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet.1985;1:425-9.

Watson L, Richardson AR, Holt RC, et al. Henoch-Schönlein purpura—a 5-year review and proposed pathway. PLoS One. 2012;7:e29512. doi:10.1371/journal.pone.0029512

Chapter 46.7
Juvenile Dermatomyositis
Priyankar Pal

Juvenile dermatomyositis (JDM) is an uncommon chronic inflammatory multisystem disease affecting predominantly the skin and striated muscles. It is characterized by symmetrical proximal muscle weakness, a heliotrope rash and Gottron's papules **(Fig. 1)** over the knuckles and elbows. It is the most common inflammatory myopathy in children. In the presteroid era, one-third children died, one-third spontaneously recovered and one-third survived with significant residual contractures and muscle atrophy. Over the last few decades, survival and outcome have improved considerably with aggressive immunosuppressive therapies. Mortality rate in children in the West is reported to be less than 3%. However, JDM is still associated with significant morbidity and mortality in our country because of the late diagnosis and even later initiation of immunosuppression.

EPIDEMIOLOGY

Incidence is reported to be 3.2 children/million/year (US National Registry) and girls are more commonly affected than the boys. Onset is usually between 4 years and 10 years, with an average age of 7 years. However, 25% of children have onset before 4 years of age. Childhood myositis does not show much racial predilection.

ETIOLOGY

Environmental Risk Factors
Like most autoimmune diseases, JDM is thought to be the result of environmental triggers in genetically susceptible individuals, leading to immune dysfunction.

Familial Dermatomyositis
There are several reports of rare occurrence of familial JDM and an increased frequency of other autoimmune diseases in families of children with JDM.

Human Leukocyte Antigen Relationships
HLA-B*08, DRB1*0301, and DQA1*0501 confer risk of myositis. The DQA1*0301 allele is an additional risk factor for JDM.

Figure 1 Gottron's papules

PATHOGENESIS

It is characterized early in its course by perivascular inflammation. Although the exact sequence in pathogenesis is uncertain, the initial event is an immune attack on muscle capillary endothelium, followed by infiltration of dendritic cells with a resulting interferon response, and upregulation of major histocompatibility (MHC) class I expression on the surface of myofibers.

CLINICAL MANIFESTATIONS

Onset is usually insidious, with development of progressive muscle weakness and pain; a more acute onset occurs in approximately one-third of children. Easy fatigability, weakness, and low-grade fever may precede actual muscle weakness by 3–6 months.

Musculoskeletal Disease
At onset, muscle weakness is predominantly proximal, and lower extremity involvement is more common. Weakness of the anterior neck flexors, back, and abdominal muscles leads to inability to hold the head upright or maintain a sitting posture and protrusion of the abdomen. The child may stop walking, be unable to dress or climb stairs. There may be associated muscle pain or stiffness. Physical examination demonstrates symmetrical weakness that is most pronounced in the proximal muscles of the shoulders and hips. There may be occasionally edema and induration in the overlying subcutaneous tissue. The muscles may be tender and Gower's sign is often present. Later in the course of disease especially with more severe disease, the distal muscles may show varying weakness. Even with severe muscle weakness, the tendon reflexes are well-preserved. Pharyngeal and palatal muscles are frequently affected resulting in difficulty in swallowing and increased risk of aspiration. Esophageal hypomotility may be associated and contributes to this difficulty. Weakness of the voice, nasal speech and nasal regurgitation are also frequent signs.

Muscle strength should be sequentially measured and recorded using a standard scale like Childhood Myositis Assessment Scale or Disease Activity Scale. Some children may have transient arthralgia or nondeforming arthritis. The presence of persistent arthritis in a patient of known JDM signifies an overlap syndrome. Children with JDM may develop early flexion contractures.

Mucocutaneous Involvement
In a majority of children, the pathognomic cutaneous abnormalities appear either simultaneously or soon after the onset of muscle weakness. The three most typical manifestations are heliotrope discoloration of the upper eyelids, Gottron's papules, and periungual erythema and capillary loop abnormalities. The heliotrope rash occurs over the upper eyelids as a violaceous, purple coloration that often is associated with a malar rash that resembles the SLE rash in its distribution but is less well demarcated. There may be associated edema of the eyelids and face. The rash varies in intensity and area of distribution and is photosensitive in 50% children **(Fig. 2)**. As already stated, there may be associated edema and induration, but severe edema is unusual and is indicative of a very severe disease **(Fig. 3)**. Later in the disease course, the skin may thin out and there may be atrophy of the subcutaneous structures with hypo/hyperpigmentation.

Gottron's papules are shiny, erythematous plaques occurring on the extensor surfaces of the joints. They are especially common over the proximal interphalangeal joints of the hands but may occasionally appear over the extensor surfaces of the elbows and knees. The periungual skin is often intensely erythematous, and careful examination with the naked eye or the lens of an ophthalmoscope documents the presence of telangiectasias. Dilatation of isolated loops, thrombosis and hemorrhage,

Figure 2 Facial telangiectatic rash

Figure 3 Gross edema of foot in severe disease

Figure 4 Calcinosis

Figure 5 X-ray showing dystrophic calcification

dropout of surrounding vessels, and tortuosity are distinctive, if not pathognomonic. There is often associated marked cuticular overgrowth which is a sign of active disease.

Dermatomyositis sine myositis or *amyopathic dermatomyositis* is rare in children. Some of them never develop myositis but others go on to develop classical JDM.

Calcinosis

Dystrophic calcification may occur in subcutaneous plaques or nodules in 12–43% of children **(Figs 4 and 5)**. Risk factors include delay in diagnosis, duration of untreated disease, inadequate therapy, and underlying cardiac or pulmonary disease. These deposits are often painful and disfiguring, may restrict movements and in severe cases, the child may be encased in an exoskeleton of calcium salts.

Systemic Involvement

The vasculopathy can involve the abdominal viscera causing ischemic pain and acute abdomen, hematemesis, melena and perforation. Cardiac involvement may manifest as sinus tachycardia, innocent murmurs or cardiomegaly. Respiratory muscle weakness results in symptomatic, restrictive pulmonary disease.

Lipodystrophy and Metabolic Abnormalities

Juvenile dermatomyositis is the most common systemic autoimmune disease associated with lipodystrophy which is characterized by slow but progressive loss of subcutaneous and visceral fat, best noticeable over the upper body and face. This is accompanied frequently by hypertriglyceridemia, insulin resistance, abnormal glucose tolerance, acanthosis nigricans, hypertension, and nonalcoholic steatohepatitis. Lipodystrophy can be focal or generalized and presents usually years after disease onset. It is common in inadequately treated individuals.

DIAGNOSIS

Traditionally, the diagnosis of JDM is based on Bohan and Peter's criteria or Rider Tagg off Criteria. The diagnosis is essentially clinical.

Criteria for Diagnosis of Juvenile Dermatomyositis
- Symmetrical weakness of the proximal musculature
- Characteristic cutaneous changes consisting of heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints, including the dorsal aspects of

metacarpophalangeal and proximal interphalangeal joints, elbows, knees, or ankles (i.e., Gottron's papules)

- Elevation of the serum level of one or more of the following skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase
- Electromyographic demonstration of the characteristics of myopathy and denervation
- Muscle biopsy documenting histological evidence of necrosis; fiber size variation, degeneration and regeneration; and a mononuclear inflammatory infiltrate, most often in a perivascular distribution

However, with the advent of muscle magnetic resonance imaging (MRI), very few rheumatologists would obtain electromyograph (EMG) or muscle biopsy unless the diagnosis is in doubt. MRI of thigh muscles demonstrating symmetrical muscle edema on T2 weighted image or short-tau inversion recovery (STIR) sequence has become the preferred diagnostic modality.

Investigations

Acute Phase Reactants
Thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein correlate with the degree of inflammation and help to differentiate inflammatory myopathies from noninflammatory disorders like muscular dystrophy.

Muscle Enzymes
Serum levels of muscle enzymes are important not only for diagnosis but also for monitoring patients undergoing treatment. Aspartate transaminase (AST), creatinine kinase (CK), lactate dehydrogenase (LDH) and aldolase should be measured at diagnosis. AST or CK may be elevated 20–40 times of normal. However, CK levels may be normal in about 20% children, particularly with a longer duration of untreated disease. LDH appears to correlate best with disease activity. Serum levels of muscle enzymes usually decrease 3–4 weeks before improvement in muscle strength and rise 5–6 weeks before clinical relapse. As a general rule, CK levels return to normal first (usually several weeks after instituting therapy); and aldolase and LDH levels return to normal the last.

Autoantibodies
Antinuclear antibodies may be positive in 10–85%. Myositis specific antibodies like anti Jo-1 are uncommon in pediatric population and occur only in about 10% of children with JDM. Anti-PM/Scl is associated with overlap syndrome.

Magnetic Resonance Imaging
Magnetic resonance imaging has dramatically replaced the need for muscle biopsy for diagnosis. The T2 weighted MR image with fat suppression demonstrates muscle edema and inflammatory changes by a hyperintense signal. MRI also helps in selecting a site for muscle biopsy.

Electromyography
Electromyography (EMG) findings that suggest inflammatory myopathy include a combination of changes of myopathy and denervation.

Muscle Biopsy
Muscle biopsy is largely performed when the diagnosis is in doubt, if there are no skin findings and sometimes to evaluate the disease activity. Biopsy usually is performed from quadriceps or deltoid,

although the best specimen may be chosen based on EMG or MRI. Muscle biopsy reveals perifascicular atrophy and variations in fiber size, as an outcome to ongoing degeneration and regeneration. Areas of focal necrosis may be noted and inflammatory infiltrates are often present.

DIFFERENTIAL DIAGNOSIS

Idiopathic inflammatory myopathies Juvenile polymyositis, overlap syndromes, cancer-associated myositis, eosinophilic myositis.

Infectious myopathies Viral (enterovirus, influenza, Coxsackie, echovirus, parvovirus, hepatitis B, human T lymphotropic virus I), bacterial and parasitic (*Staphylococcus, Streptococcus*, toxoplasmosis, trichinosis, lyme borreliosis).

Noninflammatory myopathies Muscular dystrophies, congenital myopathies, myotonic disorders, metabolic myopathies—glycogen storage diseases, lipid myopathies, periodic paralyses, mitochondrial myopathies, endocrinopathies.

Systemic rheumatic diseases Systemic lupus erythematosus, scleroderma, juvenile idiopathic arthritis, mixed connective tissue disease, vasculitis.

Mimicking cutaneous conditions Psoriasis, eczema, allergy.

Others Trauma, toxins, drug-induced myopathies, disorders of neuromuscular transmission.

MANAGEMENT

Pharmacotherapy along with early individualized physiotherapy are the mainstays of management.

Remission Induction
This is usually achieved by intravenous pulse methylprednisolone 30 mg/kg/day for 3–5 days or oral prednisolone 2 mg/kg/day for 4 weeks. Methotrexate 15–20 mg/m^2/week may be started concomitantly, orally or subcutaneously, in severe cases. Combined initiation of corticosteroids and methotrexate has synergistic action and gives the liberty of tapering steroids early without risking a disease flare.

Maintenance
Therapy during this phase consists of oral prednisolone which is initially given at a dose of 1 mg/kg/day and then gradually tapered off over a period of 2 years depending on the clinical response. In case of disease exacerbation on tapering, low dose maintenance steroids may be continued for years. Methotrexate is continued during this phase and helps in reducing the dose of steroids. Oral hydroxychloroquine a dose of 3-6 mg/kg/day may be added along with oral prednisolone and methotrexate. This is particularly useful for skin disease in JDM. Photoprotective measures like full sleeved cotton clothing and sunscreen lotion and calcium and vitamin D supplementation for bone protection are given to most patients.

Second Line Therapies
Whereas majority of patients will show good response to steroids with or without methotrexate, some patients do need second line treatments. These consist of intravenous immunoglobulin at 2 g/kg/month, cyclosporine at 2.5–7.5 mg/kg/day, azathioprine at 1–3 mg/kg/day or combinations of the above. Third line drugs are less frequently needed and consist of monthly pulses of intravenous cyclophosphamide, mycophenolate mofetil, tacrolimus or biologicals like Rituximab, Etanercept or Infliximab. Second and third line therapies are reserved for refractory patients or those with unacceptable toxicities to first line drugs.

Management of Complications

Calcinosis

There is no accepted effective therapy but general agreement is that early aggressive therapy with corticosteroids and other medicines results in decreased frequency and severity of calcinosis. Medications like colchicine, aluminum hydroxide, diphosphonates and recently tumor necrosis factor blockade have shown variable benefits.

Lipodystrophy

Recent data have suggested leptin deficiency as an important causative factor and trials administering recombinant human leptin have shown promising results.

Monitoring

Success of therapy is evaluated using the following parameters:
- Abatement of systemic signs and symptoms
- Improvement in muscle strength (preferably tested by single observer)
- Regression of acute inflammatory markers
- Improvement in muscle enzymes
- Sometimes by imaging modalities like MRI or muscle ultrasound.
- Systemic symptoms and fever usually abate within a few days and muscle enzymes decrease appreciably by 1–2 weeks of initiation of therapy. However, improvement in muscle strength and dermatitis occurs over months.

PROGNOSIS

Majority of patients have a uniphasic disease course with good functional outcome. About 30% survive with minimal atrophy or contractures. A few develop lipoatrophy and insulin resistance and some evolve into mixed connective tissue disease. Mortality is about 1-2% and usually occurs within the first 2 years of onset due to respiratory insufficiency, acute gastrointestinal hemorrhage, myocarditis or interstitial lung disease.

IN A NUTSHELL

1. Juvenile dermatomyositis is the most common inflammatory myopathy of childhood.
2. Clinical features, if present, are characteristic and help in diagnosis. Skin changes include Gottron's papules and heliotrope rash. Muscle changes include features of proximal muscle weakness with inflammation.
3. MRI of muscles showing inflammation and edema helps in diagnosis. Muscle biopsy is usually reserved for children where clinical features are not characteristic.
4. Lipodystrophy and calcinosis are two most important long-term complications, and may progress despite therapy.
5. Immunosuppression with steroids and an additional steroid sparing agent is the mainstay of therapy. Early diagnosis and effective therapeutic regimen help in reducing the risk of calcinosis.

MORE ON THIS TOPIC

Chickermane PR, Mankad D, Khubchandani RP. Disease patterns of juvenile dermatomyositis from Western India. Indian Pediatr. 2013;50(10):961-3.

Chowdhary V, Wakhlu A, Agarwal A, Misra R. Outcome in juvenile dermatomyositis. Indian Pediatr. 2002;39(10):931-5.

Ravelli A, Trail L, Ferrari C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. Arthritis Care Res (Hoboken). 2010;62(1):63-72.

Singh S, Kumar L, Shankar KR. Juvenile dermatomyositis in north India. Indian Pediatr. 1997;34(3):193-8.

Stringer E, Bohnsack J, Bowyer SL, et al. Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey. J Rheumatol. 2010;37(9):1953-61.

Chapter 46.8
Systemic Lupus Erythematosus: Clinical Manifestations

Sathish Kumar

Systemic lupus erythematosus in children (pSLE) is a multisystem autoimmune disease with a greatly variable clinical presentation and course. Frequently, children with SLE present with systemic constitutional symptoms like fever, fatigue, alopecia, weight loss, lymphadenopathy and hepatosplenomegaly. In pSLE, skin, musculoskeletal and renal systems are the most common organ systems involved. Gastrointestinal disease, liver involvement, myositis and myocarditis are rare in children. Because SLE is a periodic illness, there is often a delay in diagnosis. In 1982, the American College of Rheumatology (ACR) published classification criteria for SLE **(Table 1)**. In 2008, Hikari et al. summarized common clinical features of pSLE in their cohort **(Table 2)**.

CLINICAL FEATURES

Mucocutaneous Involvement

About 50–80% of children with SLE have skin involvement at the time of diagnosis and up to 85% of patients during the course of the disease. Classically three rashes are described in the ACR classification criteria. The malar or *butterfly* rash is the most common cutaneous manifestation and hallmark of the disease. It develops over malar eminences and crosses the nasal bridge and spares the nasolabial folds **(Fig. 1)**. The forehead and chin also may be affected. Malar rash can appear as a blush or a maculopapular eruption with associated scaling and usually is not pruritic. A similar rash may be seen in dermatomyositis; however, Gottron's papules on the metacarpophalangeal and interphalangeal joints, elbows, and knees are not seen in SLE and this feature helps distinguish the two.

Discoid lupus lesions are present in association with SLE in approximately 5–10% of patients who have pSLE **(Fig. 2)**. Discoid lupus, named after its coin shape, is an erythematous rash that primarily affects the face, ears, and scalp, although the upper extremities, upper chest and back may be affected. The rash may scale or crust. The central area may be hypopigmented, whereas the active border may appear hyperpigmented. The lesions may heal with a scar or atrophy, and discoid patches on the scalp may result in a scarring alopecia if the hair follicles are damaged. Isolated discoid lupus erythematosus without systemic involvement is rarely seen in the pediatric age group.

Vasculitic rashes present as palmar erythema and tender skin nodules **(Fig. 3)**, purpura, or ulcerations on fingers or toes, pinnae, or nares. Severe ulcerating lesions may signify more significant disease activity in other organs, whereas the appearance or reappearance of a malar rash often heralds a disease flare. Hard palate ulceration is usually painless. Erythematous ulcer is sign of active disease.

Raynaud phenomenon occurs less commonly in pediatric than in adult SLE. Triphasic color change (blue, white, and, on rewarming, red) of the hands or feet, occasionally on the ears or nose occurs in classical Raynaud's phenomenon. The affected area becomes pale and painful, then cyanotic, and on rewarming, erythematous. There may be an associated tingling or burning sensation, especially during the rewarming, erythematous phase. Exposure to cold, caffeine and extreme emotion triggers Raynaud's phenomenon. Patients should avoid those triggers and pay

Table 1 1982 Revised Criteria for Classification of SLE*

1.	Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2.	Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.	Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4.	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5.	Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6.	Serositis	*Pleuritis:* Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
7.	Renal disorder	Persistent proteinuria > 0.5 g/day or > 3+ if quantitation not performed OR Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8.	Neurologic disorder	*Seizures:* In the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR psychosis, in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, electrolyte imbalance
9.	Hematologic disorder	Hemolytic anemia with reticulocytosis OR leukopenia: < 4000/mm^3 on two or more occasions OR lymphopenia: < 1500/mm^3 on two or more occasions OR thrombocytopenia: < 100,000/mm^3 in the absence of offending drugs
10.	Immunologic disorder	Positive LE cell preparation OR anti-DNA: antibody to native DNA in abnormal titer OR anti-Smith antibody: presence of antibody to Sm nuclear antigen OR false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11.	Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
Reproduced from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11): 1271-7.

attention to keeping the body core and the extremities warm by multiple layer clothing and gloves.

Livedo reticularis occurs in less than 10% of patients with pSLE. It erupts as a reddish-purplish lacy rash, usually on the extremities or torso and often is associated with the presence

Table 2 Clinical features of SLE at presentation*

Organ system involvement	At diagnosis (%) (n = 256)	Within 1 year after diagnosis (%) (n =256)	Ever (%) (n = 256)
Mucocutaneous involvement			
• Malar rash	155 (61)	161 (63)	169 (66)
• Other rash	96 (38)	106 (41)	111 (43)
• Oral ulcers	55 (21)	59 (23)	76 (30)
• Alopecia	56 (22)	62 (24)	73 (29)
• Photosensitivity	44 (17)	45 (18)	52 (20)
• Nasal ulcers	21 (8)	25 (10)	26 (10)
• Digital ulcers	9 (4)	10 (4)	13 (5)
Nephritis*	95 (37)	117 (46)	141 (55)
• Mesangial (class II)	14 (15)	21 (18)	25 (18)
• Focal proliferative (class III)	27 (28)	36 (31)	41 (29)
• Diffuse proliferative (class IV)	45 (47)	50 (43)	65 (46)
• Membranous (class V)	15 (16)	20 (17)	29 (21)
Nephrotic syndrome	20 (22)	22 (19)	25 (18)
CNS	40 (16)	53 (21)	68 (27)
• Lupus headache	23 (58)	31 (58)	42 (62)
• Psychosis	14 (35)	21 (40)	25 (37)
• Cerebrovascular disease	13 (33)	14 (26)	20 (29)
• Cognitive dysfunction	9 (23)	13 (25)	15 (22)
Cardiac			
• Pericarditis	30 (12)	33 (13)	39 (15)
• Myocarditis	3 (1)	5 (2)	6 (2)
• Endocarditis	0	0	1 (0.4)
Pulmonary			
• Pleuritis	30 (12)	32 (13)	37 (14)
• Pneumonitis	1 (0.4)	1 (0.8)	2 (0.8)
Myositis	8 (3)	8 (3)	9 (4)
Diffuse lymphadenopathy	48 (19)	50 (20)	51 (20)
Others			
• Raynaud's	35 (14)	45 (18)	49 (19)
• Thrombotic thrombocytopenic purpura	2 (0.8)	2 (0.8)	2 (0.8)
Constitutional symptoms			
• Fatigue	129 (50)	136 (53)	142 (55)
• Fever	101 (39)	104 (41)	106 (41)
• Weight loss	74 (29)	79 (31)	82 (32)
• Anorexia	51 (20)	72 (28)	72 (28)
• Headache	34 (13)	39 (15)	(18)

Reproduced from Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, et al. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. J Pediatr. 2008;152(4):550-6.

Figure 1 Malar rash with chin involvement in a patient who has pediatric systemic lupus erythematosus

Figure 2 Discoid lupus erythematosus lesion on the forehead

Pain amplification syndrome secondary to a sleep disturbance or mood change as a result of the glucocorticoid therapy can occur.

Renal Involvement

Renal disease is the greatest contributor to morbidity and mortality in the pSLE. Lupus nephritis has been reported in 29–80% of pediatric SLE cases in various studies. Up to 85% of patients with pSLE are affected, usually within the first year of diagnosis. Renal involvement manifests as proteinuria, microscopic hematuria, hypertension, or elevated blood urea nitrogen and creatinine level. Immune complexes involving DNA and anti-double stranded DNA (dsDNA) get deposited in the mesangium and subendothelial space, leading to activation of complement and influx of inflammatory cells. These pathological changes manifest histologically as mesangial, focal, or diffuse proliferative glomerulonephritis, and clinically with active urine sediment (red blood cells, white blood cells, and cellular and granular casts), low complement levels (C3, C4), elevated anti-dsDNA levels, and proteinuria. A spot first-morning UP:UC ratio (urine protein-to-creatinine ratio) often is used as an indicator of proteinuria and active renal disease.

Because class and severity of the renal disease guides treatment, biopsy results play a major role in determining therapy. A renal biopsy with histologic, immunofluorescent, and electron

of antiphospholipid antibodies. Alopecia may be one of the presenting manifestations of the disease. It occurs classically in the frontal area but can be diffuse. As the disease activity comes down, patients usually grow new hair.

Musculoskeletal Involvement

Arthralgia and arthritis are very common in pSLE. Unlike in juvenile idiopathic arthritis, SLE arthritis usually is nonerosive. Arthritis presents as symmetrical involvement of both the large and small joints, primarily involving the knees, wrists, ankles, and fingers. The arthritis seen in pSLE is painful in approximately 50% of patients, whereas in the other half, it is relatively asymptomatic. The affected joints usually have only mild to moderate joint effusions; however, significant joint-line tenderness and painfully reduced range of movement may be present. Myalgia and myositis are less common in pSLE.

Figure 3 Vasculitic rash over both palms in a patient who has pediatric SLE

Table 3 International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis*

Lupus nephritis class	Description
Class I[a]	Minimal mesangial lupus nephritis
Class II[b]	Mesangial proliferative lupus nephritis
Class III[c]	Focal lupus nephritis
• Class III (A)	Active lesions, focal proliferative lupus nephritis
• Class III (A/C)	Active and chronic lesions, focal proliferative and sclerosing lupus nephritis
• Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV[d]	Diffuse lupus nephritis
• Class IV-S (A)	Active lesions, diffuse segmental proliferative lupus nephritis
• Class IV-G (A)	Active lesions, diffuse global proliferative lupus nephritis
• Class IV-S (A/C)	Active and chronic lesions, diffuse segmental proliferative and sclerosing lupus nephritis
• Class IV-G (A/C)	Active and chronic lesions, diffuse global proliferative and sclerosing lupus nephritis
• Class IV-S (C)	Chronic inactive lesions with glomerular scars: diffuse segmental sclerosing lupus nephritis
• Class IV-G (C)	Chronic inactive lesions with glomerular scars: diffuse global sclerosing lupus nephritis
Class V[e]	Membranous lupus nephritis
Class VI[f]	Advanced sclerosing lupus nephritis

[a] Normal glomeruli by light microscopy, but mesangial immune deposits by IF.
[b] Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
[c] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
[d] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis, when ≥ 50% of the involved glomeruli has segmental lesions, and diffuse global (IV-G) lupus nephritis, when ≥ 50% of the involved glomeruli have global lesions. A segmental lesion is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
[e] Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations; class V lupus nephritis may occur in combination with class III or IV, in which case both are diagnosed; class V lupus nephritis may show advanced sclerosis.
[f] Ninety percent or more of glomeruli globally sclerosed without residual activity.
* Reproduced from Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15(2):241-50.

microscopic analysis is necessary to classify the histologic type of renal disease. The International Society of Nephrology (ISN) and the Renal Pathology Society have revised the original World Health Organization classification of renal biopsy findings in SLE into six different classes **(Table 3)**. Patients may change from one class to another either before or during treatment.

Minimal mesangial lupus nephritis (Class I) is the mildest form of nephritis. These children have a normal urinalysis and creatinine level. This class does not require specific treatment and generally has a good prognosis. Approximately 25% of patients with pSLE will have *mesangial proliferative lupus nephritis (Class II).* These patients may have microscopic hematuria or proteinuria. This class also does not require specific treatment. This class of renal disease is considered very mild, but there is always a risk of progression. *Focal proliferative lupus nephritis (Class III)* often presents with hematuria and proteinuria. Nephrotic syndrome, hypertension, and abnormal blood urea nitrogen and creatinine levels may be prevalent. *Diffuse proliferative lupus nephritis (Class IV)* is the most common and most severe type of lupus nephritis. Patients present with hematuria, proteinuria, hypertension, low C3 and C4 levels and elevated anti-dsDNA levels. This class is similar to class III with the major difference being that more than 50% of glomeruli have evidence of active proliferation. The most significant lesions associated are widespread subendothelial immune deposits and proliferation of the mesangial cells. *Membranous nephritis (Class V)* occurs in 10–20% of patients who have renal disease. These children usually have nephrotic range proteinuria without hematuria. Class V nephritis may be seen in conjunction with another renal lesion.

The current ISN classification allows for patients to have Class II, III, or IV nephritis in addition to Class V nephritis and to be classified as having both. The prognosis of patients who have Class V nephritis in the presence of Class III or Class IV nephritis is the same as patients who have isolated Class III or IV nephritis.

Renal vasculitis occurs in less than 10% of patients who have renal lupus. When present, it is most commonly a thrombotic microangiopathy.

Renal flares are common during the disease course of lupus nephritis. Flares can be frequently detected by increasing proteinuria before the recurrence of constitutional symptoms like fever, weight loss, increasing hair loss and oral ulcers. Many follow-up studies have shown that the natural history of Class III and Class IV nephritis is to flare. The overall renal outcome of children who have lupus nephritis has improved significantly during the past decades. The recent 5-year renal survival rates for Class IV lupus nephritis are 88–93%. The reported 10-year renal survival rate is 85%.

Neuropsychiatric Involvement

Neuropsychiatric systemic lupus erythematosus (NP-SLE) is the involvement of the CNS and the peripheral nervous system. NP-SLE occurs in 20–70% of pSLE patients. NP-SLE is the second leading cause of morbidity and mortality after renal involvement. In 1999,

the American College of Rheumatology classified neuropsychiatric involvement into 19 separate disease entities **(Table 4)**. Headache is the most common neuropsychiatric manifestation. A true lupus headache is refractory to standard analgesic treatment. It usually requires narcotic analgesia. Psychosis occurs in 30–50% of pSLE children. Characteristically, the hallucinations have features of an organic psychosis, including visual or tactile hallucinations. Suicidal ideation is common.

Decreased concentration and cognitive dysfunction, psychosis, seizures, transverse myelitis, central nervous system vasculitis, or stroke are the other most common neuropsychiatric manifestations. Indeed, SLE can cause almost any neurologic disorder. Cerebrovascular disease occurs in 12–30% of cases. When present, cerebrovascular disease usually involves the microcirculation, and therefore angiographic studies are usually normal except in the presence of a stroke. Headaches and seizures are the most common clinical signs and symptoms of CNS vasculitis.

Peripheral Nervous System

In pSLE, cranial and peripheral neuropathies occur infrequently. pSLE patients may present with optic neuropathy and oculomotor palsy and less frequently with facial palsy, trigeminal neuropathy, or nystagmus and vertigo. Transverse myelitis may present with acute paraplegia or quadriplegia and may be the presenting sign of SLE. Autonomic nerve dysfunction occurs in up to 50% of adults who have SLE but is rare in children.

Hematologic Involvement

Anemia, thrombocytopenia, and leukopenia are seen in 50–75% of patients. The most common anemia is normochromic normocytic anemia. When SLE is systemically active, mild anemia is frequently present. The Coombs test is positive in approximately 30–40% of patients, but only less than 10% of patients have overt hemolysis. pSLE children present with anemia requiring blood transfusion with jaundice and splenohepatomegaly.

Thrombocytopenia may be the initial presentation in up to 15% of pediatric cases. Children present with spontaneous mucocutaneous bleeding or menorrhagia. Children who have chronic autoimmune idiopathic thrombocytopenic purpura (AITP) should be assessed for the presence of antinuclear antibodies. If present, they are at high-risk for developing SLE.

Table 4 Nomenclature and case definitions for neuropsychiatric lupus syndromes

Central nervous system	Peripheral nervous system
• Aseptic meningitis • Cerebrovascular disease • Demyelinating syndrome • Headache (including migraine and benign intracranial hypertension) • Movement disorder (chorea) • Myelopathy • Seizure disorders • Acute confusional state (< 1%) • Anxiety disorder • Cognitive dysfunction (55–80%) • Mood disorder (14–57%) • Psychosis (0–8%)	• Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome) • Autonomic disorder • Mononeuropathy (single/multiplex) • Myasthenia gravis • Cranial neuropathy • Plexopathy • Polyneuropathy

Reproduced from The American College of Rheumatology. Nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42(4):599-608.

Leukopenia is seen in 20–40% of cases of pSLE. Both lymphopenia and granulocytopenia can be present, but lymphopenia is more common. Lymphopenia is a sensitive marker of general disease activity and does not require specific therapy.

Antiphospholipid antibody syndrome (APLS) secondary to SLE manifests as thrombocytopenia, arterial or venous thrombosis, stroke, transient ischemic attack, chorea and avascular necrosis. Laboratory abnormalities include positive lupus anticoagulant (LA), elevated anticardiolipin and anti-beta2 glycoprotein 1 antibodies. Patients with a positive LA are especially at risk for deep vein thrombosis, thromboembolism and stroke. Patients with lupus who have anticardiolipin antibodies have twice the risk of venous thrombosis, and patients with a positive LA have 6 times the risk of venous thrombosis compared with patients with SLE without these antibodies.

Pulmonary Involvement

Pulmonary involvement occurs in 25–75% of pSLE cases. The clinical spectrum includes pleuritis, pneumonitis, infectious pneumonia, pulmonary hemorrhage, pulmonary hypertension, and pneumothorax. Uncommon manifestations are diaphragm involvement (including shrinking lung syndrome), vasculitis and pulmonary embolus. Severity of pulmonary involvement ranges from asymptomatic abnormalities of pulmonary function tests to severe life-threatening pulmonary hemorrhage. The most common manifestation is pleuritis. Children present with breathing difficulty or chest pain. The pleuritis is almost always bilateral. When the pleuritis is mild, it settles with NSAIDs. Rarely is high-dose steroid therapy required for severe disease.

Cardiac Involvement

Symptomatic pericarditis with pericardial effusion is the most common cardiac manifestation, occurring in approximately 15–25% of patients; up to 68% of patients have echocardiographic abnormalities consistent with pericarditis. Less commonly, endocarditis or myocarditis or valvular disease occurs and rarely ischemic heart disease may result secondary to coronary artery vasculitis. Valvular heart disease may be associated with the presence of antiphospholipid antibodies and noninfective or Libman-Sacks endocarditis. Lupus pericarditis can be treated with NSAIDs alone for mild cases and with the addition of corticosteroids for large effusions or severe pain.

Gastrointestinal and Liver Disease

Gastrointestinal involvement occurs in 20–40% of patients. Abdominal pain can result from peritoneal inflammation (serositis), vasculitis, pancreatitis, malabsorption, pseudo-obstruction, paralytic ileus, or direct bowel wall involvement (enteritis). Lupus enteropathy may present as acute ischemic enteritis or a protein losing enteropathy. Bowel wall inflammation presenting as cramping abdominal pain and diarrhea can reflect enteritis or may be secondary to a mesenteric vasculitis or thrombosis. Patients who have gastrointestinal vasculitis are at risk for perforation. The signs and symptoms may be masked by the use of high-dose steroids.

Pancreatitis is uncommon, with an overall incidence of less than 5%, and may reflect active disease, an infectious complication, or be secondary to drug therapy like steroids or azathioprine. Splenomegaly occurs in 20–30% of pediatric cases. Functional asplenia is common and increases the risk for sepsis. Hepatomegaly occurs in 40–50% of patients and up to 25% have abnormal liver function tests. Markedly elevated liver function

tests can be seen in lupoid hepatitis, whereas mild abnormalities of liver function tests are commonly seen.

Endocrine Involvement

Hypothyroidism is the most common endocrine involvement in SLE. Up to 35% of pSLE patients have antithyroid antibodies but only 10–15% of patients develop overt hypothyroidism. Hyperthyroidism has been described rarely. Diabetes mellitus may develop as a result of corticosteroid use and obesity. Delayed puberty is common. Irregular menses frequently are related to active disease and usually resolve when the disease is controlled.

NEONATAL LUPUS ERYTHEMATOSUS

Neonatal lupus erythematosus (NLE) is a syndrome that occurs in 1% infants who experience transplacental passage of maternal anti-Ro/SSA and anti-La/SSB antibodies. NLE is characterized by a photosensitive skin rash and congenital heart block. The mother of an infant who has NLE may have SLE or another connective tissue disorder, but 50–60% of mothers are asymptomatic.

A photosensitive, annular, erythematous rash is typical of NLE **(Fig. 4)**, although lesions suggestive of discoid lupus also occur. The skin manifestations of NLE may begin hours to days after delivery and usually resolve by 6 months of age, corresponding to the time that maternally derived IgG antibodies disappear. The appearance of the rash may be delayed until the first sun exposure. Congenital complete heart block (CCHB) from antibody-mediated damage to the conducting system is the most dreadful complication, and may be seen in up to 30% of infants born with NLE. It is permanent. Fetal bradycardia is the first sign of NLE and must be evaluated at 16 weeks gestation and at continuing intervals throughout pregnancy. Mothers should be started on dexamethasone as soon as a fetus is identified as having heart block to decrease maternal antibodies and inflammation of the conducting system and to delay the onset of fibrosis. CCHB may result in congestive heart failure in utero and hydrops fetalis. Other clinical manifestations of NLE include thrombocytopenia, leukopenia, hemolytic anemia, and neonatal hepatitis. With the exception of CCHB, the signs and symptoms of NLE usually resolve without permanent sequelae.

MORE ON THIS TOPIC

Agarwal I, Kumar TS, Ranjini K, et al. Clinical features and outcome of systemic lupus erythematosus. Indian Pediatr. 2009;46(8):711-5.

Benseler SM, Silverman ED. Systemic lupus erythematosus. Pediatr Clin North Am. 2005;52(2):443-67

Chopra YR, Yadav SP. Systemic lupus erythematosus in children: the Indian story. Indian Pediatr. 2013;50(9):886.

Gilliam BE, Ombrello AK, Burlingame RW, et al. Measurement of autoantibodies in pediatric-onset systemic lupus erythematosus and their relationship with disease-associated manifestations. Semin Arthritis Rheum. 2012;41(6):840-8.

Habibi S, Saleem MA, Ramanan AV. Juvenile systemic lupus erythematosus: review of clinical features and management. Indian Pediatr. 2011;48(11):879-87.

Hagelberg S, Lee Y, Bargman J, et al. Long-term follow-up of childhood lupus nephritis. J Rheumatol. 2002;29(12):2635-42.

Kumar K, Kole AK, Karmakar PS, Ghosh A. The spectrum of thyroid disorders in systemic lupus erythematosus. Rheumatol Int. 2012;32(1):73-8.

Mina R, von Scheven E, Ardoin SP, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2012;64(3):375-83.

Olfat MO, Al-Mayouf SM, Muzaffer MA. Pattern of neuropsychiatric manifestations and outcome in juvenile systemic lupus erythematosus. Clin Rheumatol. 2004;23(5):395-9.

Ramirez Gomez LA, Uribe Uribe O, Osio Uribe O, et al. Childhood systemic lupus erythematosus in Latin America: the GLADEL experience in 230 children. Lupus. 2008;17(6):596-604.

IN A NUTSHELL

1. Systemic lupus erythematosus is a periodic disease hence frequently leading to delay in diagnosis.
2. Skin, musculoskeletal and renal systems are the most common organ systems involved in pSLE. Gastrointestinal disease, significant liver involvement, myositis, and myocarditis are rare in children.
3. Malar or butterfly rash is the most common cutaneous manifestation and hallmark of the disease.
4. Isolated discoid lupus erythematosus without systemic involvement is rarely seen in the pediatric age group.
5. Arthritis is symmetric polyarthritis affecting large and small joints. It is usually nonerosive and nondeforming.
6. International Society of Nephrology and the Renal Pathology Society have revised the original World Health Organization classification of renal biopsy findings in SLE into six different classes.
7. Headache is the most common neuropsychiatric manifestation. A true lupus headache is refractory to standard analgesic treatment requiring narcotic analgesia.
8. Antiphospholipid antibody syndrome (APLS) secondary to SLE manifests as thrombocytopenia, arterial or venous thrombosis, stroke, transient ischemic attack, chorea or avascular necrosis.
9. Up to 35% of pSLE patients have antithyroid antibodies, with 10–15% of patients developing overt hypothyroidism.
10. Mother of an infant who has NLE may have SLE or another connective tissue disorder, but 50–60% of mothers are asymptomatic.

Chapter 46.9
Management of Systemic Lupus Erythematosus
Aruna Bhat

Past two decades have seen rapid improvement in the overall survival rates in patients with systemic lupus erythematosus (SLE). The change has been made possible partly due to increasing awareness enabling early identification of the disease and partly due to advances in basic science and immunology, lending way to introduction of more effective treatment agents. However, the challenges one faces in investigating, diagnosing and managing these patients are many. There is wide variation in the way the disease manifests and hence demands individualized modifications to the treatment delivered. A number of different factors need to be carefully considered before coming up with an effective management plan for each patient with SLE. This chapter focuses on investigations and management strategies in patients with SLE.

INVESTIGATIONS

During the work-up of a possible case of SLE, number of different investigations may need to be carried out. Some of them are simple and others specialized, depending on the presenting symptoms. Unless one approaches these investigations in a systematic way, the results may not only appear confusing, but also put financial strain on the patient. The role of investigations extends beyond elimination of differentials in diagnosis to identification of extent and severity of organ involvement and associated comorbidities. It is highly advisable to seek expert opinion at this stage if possible. Investigations will need to be carried out at regular intervals to monitor the disease and during episodes of acute illness. Although no one panel of tests can be prescribed to suit every patient, some of the commonly employed simple and specialized tests are enumerated below**.**

Common Laboratory Tests

Complete blood count Anemia may occur due to chronic illness or due to autoimmune destruction. Leucopenia with lymphopenia and thrombocytopenia may be commonly encountered in active SLE.

Acute phase reactants Active SLE may often have high ESR but normal CRP. High CRP should in fact alert one towards possible infection, serositis or arthritis.

Biochemistry Renal function tests, liver function tests, bone profile, and muscle enzymes.

Urine analysis Urine routine examination to monitor urinary protein and microscopic blood is important, as renal involvement is a common cause of morbidity associated with SLE in children. Spot urinary protein creatinine ratio (PCR) quantifies the amount of proteinuria when present. Persistence of protein and/or blood, in the absence of infection, qualifies for specialist nephrologist opinion and renal biopsy.

Others Thyroid function tests, direct agglutination test, lipid profile are generally checked at diagnosis and then annually.

Immunological Tests

Complements C3 and C4 are tested commonly and show decrease in levels during active SLE.

Antinuclear antibody Antinuclear antibody (ANA) is positive in more than 95% of the SLE patients. In the remaining few, it is generally felt that faulty dilution technique or method of detection are the culprits. One should refrain from using ANA test as a general screening test, but rather do it when there is high index of suspicion of SLE. It is because ANA test has high false positivity and may be seen in low titers in number of different conditions and in a subset of normal healthy individuals. It is the negative predictive value of this test that is more contributory in SLE than the positive predictive value. The two popular methods available to detect ANA are enzyme linked immunosorbent assay (ELISA) and immunofluorescence assay (IFA). IFA has added advantage of providing details such as antibody titers and patterns of staining which may aid in diagnosis. A titer higher than 1:160 with a homogenous staining pattern is highly predictive of SLE in a clinically suggested case.

Extractable nuclear antigens/Antinuclear antibody profile test The extractable nuclear antigens (ENA) panel detects different autoantibodies to subcellular structures. The test is carried out only when the ANA test is positive in high titers. The pattern of positive and negative antibodies on the panel provides important clues in differentiating SLE from other connective tissue disorders. Among the antibodies, anti-Smith (anti-SM), and anti-double-stranded DNA antibody (anti-dsDNA) antibodies are highly specific for SLE. Anti-Sm antibodies are seen in about 30% of SLE patients and dsDNA antibodies in about 70% of the cases. Other autoantibodies that may be seen in SLE are anti-RNP, anti SS-A and anti SS-B, anti-proliferating cell nuclear antigen (anti-PCNA) and anti-ribosomal–P antibodies.

Antiphospholipid antibodies Some SLE patients may have associated antiphospholipid antibodies. These patients may develop higher morbidity due to recurrent thrombotic tendencies, renal and neuropsychiatric complications and pregnancy related complications. Lupus anticoagulant, anticardiolipin antibodies and β2-glycoprotein antibodies are forms of antiphospholipid antibodies that can be tested. Aspirin prophylaxis, or at times anticoagulation may be required if the presence of these antibodies is a cause for concern.

Other tests in select patients Renal ultrasound and biopsy with immunohistochemistry; Magnetic resonance imaging (MRI) brain, Magnetic resonance angiography (MRA) brain; pulmonary function tests, chest radiography, computed tomography of chest, ECHO, ECG, psychometric tests; skin biopsy, nerve biopsy, electromyography; ophthalmology assessment; radiographic examination of spine, bone mineral density scan (DEXA).

DIAGNOSIS

Diagnosis is based on the findings obtained from detailed history, physical examination, supportive lab, imaging and biopsy findings. For the purpose of carrying out collaborative trials, classification criteria for SLE have been defined by American College of Rheumatology (ACR) and by Systemic Lupus International Collaborating Clinics (SLICC), taking into consideration both clinical and immunological findings. Although these criteria may help in diagnosis, it is to be strictly remembered that they are meant for classification and case definition. Waiting for fulfillment

of criteria for confirmation of diagnosis may dangerously delay the necessary treatment.

TREATMENT

Treatment plans that currently exist are largely based on observational studies and extrapolated data from adult studies. Large scale international collaborative trials are needed for evidence based treatment guidance. Treatment regimens adopted by different centers may vary but overall format of care remains similar.

Treatment of Systemic Lupus Erythematosus with No Major Organ Involvement or Life-threatening Features

To achieve immediate and adequate control of inflammation, oral corticosteroids in low dose (less than 0.35 mg/kg/day) are often employed early in the treatment for variable duration. Hydroxychloroquine has gained attention in treatment of SLE and is now recommended for treatment of all SLE patients as adjunctive therapy, unless contraindicated. The drug is particularly useful in skin and joint disease and is used at the dose of 5–6.5 mg/kg/day (generally used as 200 mg in children instead of adult maximum of 400 mg). Apart from disease modifying effect, the drug's lipid lowering effect makes it ideal for treatment in SLE. Regular 6 monthly ophthalmology screening is advised as the drug can cause ocular complications. Low-dose methotrexate at 5–10 mg/m^2 orally or subcutaneously can be added if required for better control of joint and skin symptoms. Continuous monitoring is important as the illness can progress in severity over time.

Treatment of Systemic Lupus Erythematosus with Major Organ Involvement and/or Life-threatening Features

Children with major organ involvement, such as renal, neuropsychiatric, pulmonary, cardiovascular or gastrointestinal, need aggressive treatment to save organs and to bring the overall inflammatory dysregulation under control. Treatment strategy is to induce remission and then maintain it using different regimens. These regimens include combinations of high-dose steroids, steroid sparing agents and other immunosuppressive strategies.

Induction of Remission

For the purpose of induction, high-dose steroids are used in combination with cyclophosphamide or mycophenolate mofetil. High-dose pulse intravenous methylprednisolone at 30 mg/kg (maximum of 1 g) for 3 consecutive days is generally used followed by tapering dose of oral steroids. Use of once weekly IV methylprednisolone 10–30 mg/kg/dose for 4–6 weeks, followed by oral weaning dose of steroids or combining methylprednisolone pulses with monthly cyclophosphamide are other alternative regimens.

Cyclophosphamide In combination with steroids, monthly intravenous cyclophosphamide (CYC) is considered as the *gold standard* treatment for induction in severe and life-threatening lupus.

High-dose CYC induction regimen The National Institute of Health protocol induction regimen consists of monthly intravenous pulse of CYC (starting at 500 mg/m^2 and increasing to 1 g/m^2, maximum of 1500 mg) for 6 months (7 doses) followed by maintenance regimen.

Low dose CYC induction regimen The more recent Euro Lupus trial, involving adult lupus patients, has shown that using low dose CYC at 500 mg IV pulses every 2 weeks for 6 doses also yields comparable control of symptoms as high dose regimen, with less risk of infection.

However, care should be taken at the time of administration of cyclophosphamide. It is important to hydrate the patient well and use mesna, pre- and post-CYC infusion, to minimize bladder toxicity. It is also important to monitor white cell counts after each pulse, as they nadir around day 10–14 and may require alterations to the subsequent dose if the counts continue to be less than 2,500 per µL. Other complications to consider while using CYC include increased risk of infections, hair loss and risk of malignancy. The feared gonadal toxicity is dependent on cumulative dose and is low in prepubertal children.

Mycophenolate mofetil (MMF) This drug is also emerging as an alternative to CYC for induction. The drug is introduced in slow increments over few weeks to reach 10–20 mg/kg per dose twice daily or 600 mg/m^2 per dose twice daily (generally given up to 2 g/day in children for 6 months) followed by maintenance dose. Abdominal pain and diarrhea are commonly reported symptoms. Slow introduction and increased division of doses may, to some extent, alleviate these symptoms. Enteric-coated mycofenolate sodium formulations may be used instead. Monitoring for cytopenia and liver dysfunction is also required while on MMF.

Maintenance of Remission

Maintenance therapy is usually started after 6 months of induction treatment and continued for a period of 2–3 years. Again, different therapeutic regimens are available. Both MMF and azathioprine are popular choices in this category. MMF and azathioprine are slowly replacing maintenance regimen using NIH protocol with cyclophosphamide pulses at the dose of 500 mg/m^2 once every 3 months for about 30 months.

Azathioprine is started at 1 mg/kg/day and increased slowly to reach a maximum of 2.5 mg/kg/day as tolerated. Although reasonably well-tolerated, side-effects include nausea, fatigue, alopecia, liver dysfunction and cytopenia. MMF is usually used at a dose of 1 g/day in divided doses as maintenance treatment. Oral hydroxychloroquine 4–5 mg/kg/day, and if required, low-dose oral steroids and methotrexate are continued during the maintenance phase.

Renal Disease in Systemic Lupus Erythematosus

Renal involvement in the form of lupus nephritis (LN) is common in children with SLE and influences treatment and overall prognosis. Careful monitoring of urine is recommended even when the patient remains asymptomatic. In very unwell patients or in those with persisting urinary sediments, hypertension and renal dysfunction, specialist opinion should be sought from a nephrologist and kidney biopsy carried out. LN has been classified into 6 classes depending on the histopathological observation. In children with LN, both histopathological classification on renal biopsy and overall disease activity in the patient are considered before selecting appropriate form of immunosuppression. Class I and II are milder forms of LN and do not need induction treatment unless associated with other major organ involvement. Class III and IV are proliferative forms of LN and need aggressive treatment, with induction followed by maintenance regimens. Class V is membranous form of LN. Although the treatment of this class is controversial, MMF and cyclosporine have shown good results. Class VI is advanced sclerotic form of LN and implies

end stage kidney failure. These patients do not benefit from immunosuppression and may need renal replacement therapy.

Treatment of Severe Refractory Lupus

Sometimes, despite treatment with standard regimens, the disease progresses relentlessly or recurs. This calls for trial of alternative strategies mentioned below.

B-lymphocyte is thought to have an important role in the pathogenesis of SLE and there are number of different drugs that are emerging to target B-cells at different levels. Rituximab is the drug most studied in this category in children so far. Rituximab has not been shown to be of benefit as first line agent in all patients with lupus, but has a role in management of refractory cases. Other modalities of treatment, such as immunoglobulin therapy, plasmapheresis, and hemopoetic stem cell transplantation are reserved for refractory cases. All these treatments are to be undertaken under expert guidance of a rheumatologist only.

General Measures in Treatment

- Using multidisciplinary team approach, patients need regular close monitoring to assess response to treatment, identify complications and to plan further treatment. Maintaining periodic disease activity and damage index scoring (such as SLEDAI/BILAG disease activity index and ACR/SLICC damage score index) help in this direction. Monitoring dsDNA and complement levels help in knowing the activity of illness and may help detect flares.

- Prompt identification and treatment of infections and flares improve the overall prognosis. Vaccination against *Pneumococcus* and influenza infections is advisable.

- Minimizing steroid use as much as possible and acting promptly on steroid induced morbidities such as growth issues, cataracts, hypertension, glucose intolerance, mood disturbances and osteoporosis, improve quality of life for the patient.

- Compliance to treatment can be a major factor in determining outcome and hence psychological support and educating the patient and family regarding the disease and its outlook cannot be underestimated at any cost.

- At this point in time, it may seem surreal to think about a cure for SLE in the near future. However, the future looks exciting and promising as the global medical and scientific community exerts endless efforts in identifying new biomarkers and targeted therapies. Biomarkers that can help identify the

disease and its complications early and categorize patients for upcoming targeted therapies. Novel biomarkers and targeted biologics together may work more effectively and transform the way in which this enigmatic disorder is managed.

IN A NUTSHELL

1. Early diagnosis and aggressive treatment is pivotal in influencing the final outcome.
2. Selection of investigations and their interpretation require good understanding of the nature of this illness and different patterns of involvement.
3. Identifying the different organ systems involved and assessing the severity at the time of diagnosis enable one to select the appropriate treatment regimen, prognosticate the disease course and guide the follow-up of these patients.
4. In order to help with the selection of treatment regimen, patient population is broadly divided into two groups: one in whom there is no major organ involvement or life-threatening features, and the other where the major organ systems may have got affected with or without life-threatening features.
5. Regular follow-up and monitoring is essential to identify and act on disease-related or treatment-associated complications. Disease flares due to identifiable or unidentifiable causes can often pose challenges in the course of this illness.
6. Apart from aiming at good control of illness, minimizing side-effects of medications, preventing secondary morbidities and facilitating growth and development as normal as possible, both physical and emotional, form important objectives of management.

MORE ON THIS TOPIC

Lehman TJA. Systemic Lupus Erythematosus (SLE) in Children: Clinical manifestations diagnosis. Available from: www.uptodate.com/contents/systemic-lupus-erythematosus-in-children. Accessed December, 2014.

Marks SD, Tullus K. Modern therapeutic strategies for paediatric systemic lupus erythematosus and lupus nephritis. Acta Paediatr. 2010;99(7):967-74.

Mok CC. Update on emerging drug therapies in systemic lupus erythematosus. Expert Opin Emerg Drugs. 2010;15(1):53-70.

Silverman E, Eddy A. Systemic Lupus Erythematosus. In: Cassidy JT, Petty RE, Laxer R, Lindsley C. Textbook of Paediatric Rheumatology. 6th ed. Philadelphia: Elsevier Saunders; 2010. pp. 315-43.

Systemic Diseases. In: Foster H, Brogan PA. Pediatric Rheumatology—Oxford Specialist Handbooks in Paediatrics. 1st ed. Oxford: Oxford University Press; 2012. pp. 226-59.

Chapter 46.10
Juvenile Scleroderma
Suma Balan

Scleroderma refers to the group of clinical conditions that are characterized by thickening and hardening of the skin with eventual fibrosis. This is classified into *localized* and *systemic* diseases which have further subclassifications based on clinical findings of skin involvement. In children, the most common presentation is of localized scleroderma. Systemic sclerosis in children is uncommon but associated with significant morbidity. Juvenile systemic sclerosis (JSSc) is a chronic multisystem connective tissue disorder characterized by sclerodermic skin changes and abnormalities of the visceral organs.

LOCALIZED SCLERODERMA

The reported incidence in described literature from the United States is 3–6/100,000 children or population. This is a condition where there is an increased collagen density causing thickening of the skin and subcutaneous tissues, rarely extending down to the muscle and bone also. The location, depth and distribution of this change has led to the classification of different types of localized scleroderma syndromes **(Table 1, Figs 1 to 5)**. Disabling pansclerotic morphea of children is a condition where large areas of the body are involved with deep involvement of skin, subcutis and entire dermis, clinically sparing the fingers/wrists/distal forearms/toes.

Pathogenesis

Scleroderma is essentially an autoimmune disease with increased T-cell activity and specific cytokine generation which stimulates fibroblasts to produce transforming growth factor Beta (TGF-β), connective tissue growth factor (CTGF), and increased adhesion molecules, which are responsible for increased collagen deposition. 5–10% of children could concomitantly have other autoimmune disorders including psoriasis, vitiligo, alopecia areata and 12–25% may report autoimmune disorders within family members.

Extracutaneous Manifestations

Despite being named as localized, a variety of extra-articular features have been noted in localized scleroderma syndromes. In a large multicentric follow-up study of approximately 750 children with localized scleroderma lesions, approximately 22.4% had various extracutaneous manifestations like articular (47.2%), neurologic (17.1%), vascular (9.3%), ocular (8.3%), gastrointestinal (GI) (6.2%), respiratory (2.6%), cardiac (1%), and renal (1%). Interestingly a significant number of these manifestations were found in areas unrelated to the primary lesion. A clinical examination and assessment for other manifestations is therefore an important aspect of the evaluation of these children.

Diagnosis

The diagnosis is often delayed because these lesions are generally slow growing and are relatively rare. A study from the UK showed an approximate delay of about 18 months for localized scleroderma and 13 months for systemic scleroderma (SSc) patients to be referred to a pediatric rheumatologist for evaluation and treatment. Depending on the location and resultant complaints, patients could present variously to general pediatrician, orthopedic surgeon, dermatologist, or plastic surgeon.

Table 1 Classification of localized scleroderma

Plaque morphea
• Morphea en plaque
• Guttate morphea
• Atrophoderma of Pasini and Pierini
Generalized morphea
Bullous morphea
Linear morphea
• Linear morphea (linear scleroderma)
• Morphea en coup de sabre
• Progressive facial hemiatrophy
Deep morphea
• Subcutaneous morphea
• Eosinophilic fasciitis
• Morphea profunda

Figure 1 Plaque morphea of inner thigh

Figure 2 Longstanding linear scleroderma with shortening and asymmetry of left lower leg

Course of the Disease

There are 3 different phases with localized scleroderma:

1. An active phase where progressive induration with violaceous border of lesions may be seen. At this point, newer lesions and extension of the initial lesion readily happens.
2. A phase of establishment where further extension often does not happen.

Figure 3 Childhood linear scleroderma of left lower limb causing reduced bulk and subcutaneous fat atrophy. Following treatment and physiotherapy, there is good functional recovery and equal limb length

Figure 5 Morphea right arm causing reduced bulk and asymmetry

3. Chronic phase of scarring and fibrosis leading to irreversible limitation of affected areas. Depending on the level of atrophy, superficial or dermal, the findings can vary between slight concavity to lack of hair growth, visible veins and overt asymmetry. Postinflammatory hyperpigmentation can also be a reason why the lesion is brought to the attention of a doctor.

Clinical presentation can be reflective of the acute lesion where hardening, induration and lack of pinchability are picked up or as a long-term consequence of fibrosis with contractures and asymmetry or due to extra-cutaneous features.

Investigations

Mild elevation of inflammatory markers in the counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can sometimes be seen, however a good number of children may not show such evidence of inflammation. Renal and liver functions are usually normal. Autoimmune serology occasionally can pick up some positive antinuclear antibodies (ANA). ANA positivity has been reported variably from 24% to 74% and the presence of anti-single stranded/antihistone and rarely anticentromere antibodies have been reported. Serum complements do not show any significant change.

Figure 4 Deep morphea causing facial asymmetry (left jaw and face)

While X-rays are not generally helpful, an MRI scan can show the level and depth of skin inflammation and aid in choosing best site for skin biopsy. Skilled ultrasound examinations under trained sonologist can detect the lesion as well as distinguish between active and inactive disease. Every patient needs to be assessed if any systemic involvement—lungs, cardiovascular system (CVS), GI tract or renal–is present at first assessment. Ophthalmological examination needs to be done to pick up associated uveitis or vasculitic changes.

Skin biopsy of appropriate depth is integral in confirmation of the diagnosis. Histological findings in the early stages of disease consist of a perivascular infiltrate of predominantly lymphocytes, plasma cells and eosinophils in the deep reticular dermis and subcutis, accompanied by thickened collagen bundles, decreased elastic fibers and swollen endothelial cells. Over time, disease damage accumulates and is represented by an increase in skin thickness, especially at the center of the lesion, sometimes leaving an ivory-colored sclerotic center. With thickened hypocellular (homogenized) collagen which replaces the previous inflammatory infiltrate around the dermal appendages, leaving behind atrophic eccrine glands and hair follicles. Capillaries are reduced in number with a fibrotic wall and narrowed lumen. The clinical outcome of these findings is reflected in dermal and subcutaneous atrophy.

TREATMENT OF LOCALIZED SCLERODERMA SYNDROMES

Assessment of Disease Activity

Several clinical scoring tools like modified Rodnan score, localized scleroderma clinical assessment tool as well as investigative modalities like ultrasonography (USG) and thermography have been used to assess disease activity but none have been validated as a reproducible clinical tool so far. Judging the severity and potential risk of deformity is important in making treatment decisions. If only a single small circumscribed superficial lesion in a not too prominent location is present, topical measures like topical corticosteroids, calcineurin inhibitors, psoralen ultraviolet A (PUVA) therapy etc. can be tried. But where there are deeper lesions (clinical + skin biopsy), where lesions traverse a joint, where there are extensive lesions or in locations where scarring can significantly cause cosmetic disfigurement, aggressive management is recommended. This includes a combination of systemic corticosteroids (bridging effect) and methotrexate given orally/subcutaneously depending on degree of aggression, age of child and compliance with swallowing tablets. Intralesional

corticosteroids can also be used but they also contribute to the possibility of subcutaneous skin atrophy. The dose of methotrexate is 10–20 mg/m^2/week or 0.5–1 mg/kg/week to a maximum of 30 mg/week. Therapy of skin lesions may also include lesional phototherapy, according to availability (NB-UVB/PUVA/UVA/UVA1), topical calcipotriol under occlusion, topical imiquimod or topical calcipotriol with betamethasone dipropionate.

Following onset of treatment, lesions show considerable improvement over 6–8 months and systemic corticosteroids can often be weaned and stopped in the early months. In resistance or inability to wean systemic corticosteroids, oral mycophenolate mofetil has been found to be successful. Treatment has to be continued for several years as the risk of relapse is high if stopped early. Very rarely, localized scleroderma can progress to SSc.

SYSTEMIC SCLERODERMA

It is a rare disease in childhood with a prevalence of 1/million children. Roughly 5% of all systemic sclerosis commence in childhood. It is associated with widespread cutaneous thickening with internal organ fibrosis. It can be of following types: (1) Diffuse cutaneous; (2) Limited cutaneous; and (3) Overlap cutaneous variety.

Diffuse cutaneous scleroderma is a disease of progressive skin thickening from distal to proximal extremities and progressive internal fibrosis associated with early internal organ involvement (lungs, heart and kidney).

Limited cutaneous scleroderma shows nonprogressive more distal peripheral skin thickening and associated with late onset internal organ involvement (lungs, malabsorption). CREST syndrome (a combination of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) is considered a limited cutaneous scleroderma.

Overlap syndrome is seen when there are features of other connective tissue diseases like dermatomyositis (heliotrope rash, Gottron's papules, proximal myopathy) or SLE (malar rash, hematological abnormalities, oral ulcers, etc.) along with systemic sclerosis.

Diagnosis

Age of onset must be less than 16 years. The most common clinical presentation in extremities are initial edematous changes followed by skin thickening, induration, loss of pliability, tapering fingers, and final clawing of the hand due to shortening and tightening of tendons. In the face, these changes cause the typical *scleroderma facies* with pinched nose, thin pursed lips, small mouth, prominent teeth, and an expressionless appearance **(Fig. 6)**. Provisional guidelines for the diagnosis of juvenile systemic sclerosis are listed in **Box 1**. Sensitivity and specificity of this classification is more than 90% when major and 2 minor criteria are present.

Raynaud's phenomenon **(Fig. 7)** is classically noted and can be differentiated from children with primary Raynaud's phenomenon who do not have digital tip ulcers, vasculopathic features and autoantibodies.

Investigations

A detailed multisystem assessment by pulmonologists, cardiologists, dermatologists, ophthalmologists, gastroenterologists and renal physicians must be undertaken at the initial visit and extent of disease as well as category of disease has to be delineated. Overlap SSc is more common in children as compared to adults and similarly renal crisis is also significantly less common in childhood disease. Musculoskeletal system involvement is more common in

Figure 6 Scleroderma facies

BOX 1 Clinical and diagnostic criteria for juvenile systemic sclerosis

A. **Major criterion** (required)

- Skin induration/thickening proximal to the MCP or MTP joints

B. **Minor criterion** (2 required) (scleroderma specific organ involvement)

- *Cutaneous*: Sclerodactyly; Raynaud's phenomenon; Nailfold capillary changes (megacapillaries and avascular areas); Digital tip ulcers
- *Gastrointestinal*: Dysphagia, GERD
- *Cardiac*: Arrhythmias; Heart failure
- *Renal*: Scleroderma renal crises, New arterial hypertension
- *Respiratory*: Pulmonary fibrosis (CXR/HRCT), Pulmonary arterial hypertension (assessed by echocardiography), Decreased DLCO
- *Neurological* : Neuropathy, Carpal Tunnel syndrome,
- *Musculoskeletal*: Tendon friction rubs, Arthritis, Myositis
- *Serological*: Antinuclear antibodies, SSc selective autoantibodies: Antitopoisomerase1 (Scl-70), anticentromere, anti-RNA polymerase 1 or 3, anti PM-Scl, anti-fibrillin

Modified from Zulian, et al. Arthritis Rheum. 2007;57:203–12.
Abbreviations: CXR, chest X-ray; DLCO, diffusing capacity of the lungs for carbon monoxide; GERD, gastroesophageal reflux disease; HRCT, high resolution computed tomography; MCP, metacarpophalangeal; MTP, metatarsophalangeal; SSC, systemic sclerosis.

Figure 7 Raynaud's phenomenon with thin shiny fingers

children as well as GI features like gastroesophageal reflux disease (GERD). Although typical autoantibodies are important in the classification of this diagnosis, 25–33% of children may only have ANA positivity with no specific autoantibody on detailed profile testing, hence lack of autoantibodies in a typical clinical setting should not eliminate the diagnosis.

Complications

All forms of SSc can be highly disabling as well as cause significant visceral complications that can be life-threatening: interstitial lung disease, pulmonary artery hypertension, etc. Cardiac complications are the most common cause of mortality in children (myocardial fibrosis and conduction defects, cardiomyopathy and pericarditis) as opposed to adults in whom lung disease related complications are the leading cause of mortality. This disease can significantly affect quality of life and daily activities, impair school attendance and compromise the overall development of the child. This can cause depression in the child and family. Family may also need significant resources—both financial and otherwise to support the child.

Treatment

Treatment has to be undertaken in a tertiary center with multi-disciplinary liaison and follow-up with all other specialists including dermatologists, pulmonologists, cardiologists, gastro-enterologists, physical medicine and rehabilitation specialists and nephrologists. Attention must be given to psychological support to child and family. General measures include use of antacids and prokinetic drugs for GI motility, vasodilators for Raynaud's phenomenon, rotating antibiotics and probiotics for malabsorption, nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis/tendinitis and physical therapy.

Specific Measures

Corticosteroids can be considered in active myositis/arthritis and other organ disease but have to be used with caution for fear of precipitation of scleroderma renal crises. Methotrexate is useful in retarding the progression of skin disease especially when diagnosed early. While cyclophosphamide is recommended for interstitial lung disease, other drugs like mycophenolate mofetil and azathioprine are increasingly gaining support due to reduced toxicity. Agents for improving calcinosis have not shown adequate benefits. ACE inhibitors are used for scleroderma induced renal crises. As of yet, adequate experience with biological medications (Rituximab) is still lacking for formal recommendations though there are reports of utility in lung disease.

Outcome

Childhood onset has a more significant outcome profile where identified early due to less internal organ involvement compared to adults. A recent study has shown 10-year survival rates to be 98% in children versus 75% in adults.

IN A NUTSHELL

1. Early recognition of localized scleroderma syndromes is necessary as they are more common in the growing age of childhood than adults. Significant morbidity due to contractures and disfigurement can exist.
2. Early onset of appropriately aggressive treatment can have an excellent outcome in most cases. However, treatment needs to be continued for several years to avoid risk of relapse.
3. Localized cutaneous scleroderma is associated in 22.5% of children with significant extracutaneous manifestations.
4. Systemic scleroderma is a rare disease but associated with significant mortality and morbidity.

MORE ON THIS TOPIC

Christen-Zaech S, Hakim MD, Afsar FS, Paller AS. Pediatric morphea (localized scleroderma): review of 136 patients. J Am Acad Dermatol. 2008;59(3):385-96

Foeldvari I, Zhavania M, Birdi N, et al. Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multi-national survey. Rheumatology (Oxford). 2000;39(5):556-9.

Hawley DP, Baildam EM, Amin TS, et al. Access to care for children and young people diagnosed with localized scleroderma or juvenile SSc in the UK. Rheumatology (Oxford). 2012;51(7):1235-9.

Kowal-Bielecka O, Landewé R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis. 2009;68(5):620-8.

Li SC, Feldman BM, Higgins GC, et al. Treatment of pediatric localized scleroderma: results of a survey of North American pediatric rheumato-logists. J Rheumatol. 2010;37(1):175-81.

Marzano AV, Menni S, Parodi A, et al. Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases. Eur J Dermatol. 2003;13(2):171-6.

Scalapino K, Arkachaisri T, Lucas M, et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. J Rheumatol. 2006;33(5):1004-13.

Tollefson MM, Witman PM. En coup de sabre morphea and Parry-Romberg syndrome: a retrospective review of 54 patients. J Am Acad Dermatol. 2007;56(2):257-63.

Torok KS. Pediatric scleroderma: systemic and localized forms. Pediatr Clin North Am. 2012;59(2):381-405.

Zulian F, Vallongo C, Woo P, et al. Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum. 2005;52(9):2873-81.

Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College Of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum. 2007;57(2):203-12.

Chapter 46.11
Antiphospholipid Syndrome
Jasmina Ahluwalia, Anju Gupta

Antiphospholipid antibody syndrome (APS) is an acquired cause of thrombophilia accounting for 20% of young patients with stroke or venous thromboembolism. It is an autoimmune disorder characterized by a combination of clinical features (thrombosis and/or recurrent pregnancy loss) and laboratory tests (positivity for one or more of the following antibodies: anticardiolipin (aCA), anti-beta 2 glycoprotein 1 (aβ_2GP1) or lupus anticoagulant (LAC). The thrombosis may be arterial or venous or small vessel, but must not be due to a vasculitic disorder. When APS occurs in the context of another disease, especially systemic lupus erythematosus (SLE), the term secondary APS is used. It may however occur in the absence of a known disease, in which case the term primary APS is used. An additional life-threatening emergency called catastrophic APS is also described, though rare in children.

Though initially APS was reported in adults; however it has now been reported in children. In the latter population, it is understandably less common, perhaps because of the rarity of defining clinical criteria in children. A large pediatric European registry reported slightly older age, higher frequency of venous thrombosis and other hematological manifestations in secondary pediatric APS as compared to primary APS. It is possible that pediatric APS remains an under diagnosed entity unless other defining clinical criteria—thrombocytopenia, etc., are included. This fascinating syndrome remains a focus of much clinical and laboratory research and from time to time, the existing literature is reviewed in workshops and specialist meetings to refine the diagnostic criteria.

The importance of establishing the diagnosis of APS rests on the fact that thrombosis is accompanied by significant morbidity, and may be recurrent or even fatal. Use of antiplatelet and anticoagulant therapy may help save life and limb. It would appear that the diagnosis of APS is straight forward since if the clinical scenario is appropriate, it is likely that positive tests for the above mentioned antibodies would imply the presence of the syndrome. However, this is not the case since with the present state of knowledge, we are not sure of the exact target of the pathogenetic antibodies and hence nonspecific positivity for the antibodies may misdirect therapy. Reporting of the APS in children from our country is limited due to variety of factors—the rarity of clinical defining criteria in children, low index of suspicion, nonavailability of tests and the need for expertise in performing the tests.

PATHOGENESIS

This autoimmune disorder is characterized by the generation of antibodies to a variety of targets. The term antiphospholipid antibody (aPL) is used for any antibody detected by assays for LAC, (aCA), or aβ_2GP1 antibodies. LAC can be directed against a plasma protein, β_2GP1 or against the coagulation protein prothrombin. A variety of mechanisms have been postulated in the generation of APS antibodies and their thrombogenic effects:

- Oxidative stress leading to formation of disulfide bonds on domain 1 of β_2GP1, rendering it immunogenic by exposing a previously hidden B-cell epitope.
- Native β_2GP1 circulates in plasma in a loop like circular configuration. When it binds to phospholipid, the molecule becomes hook-shaped, leading to exposure of an antigenic site.
- Reduced activity of endothelial nitric oxide synthase, due to aβ_2GP1 antibodies leading to impaired vascular relaxation.

- Enhanced tissue factor activity by aβ_2GP1 antibodies, promoting thrombogenesis.
- Increased platelet activation on binding of β_2GP1 to vWF factor and GpIα receptor on the platelet surface. These two are cross-linked by the aβ_2GP1 antibody and lead to increased platelet adhesiveness.
- Upregulation of toll like receptor 7 and 8 in patients with immune disorders.
- Disruption of the protective annexin shield on the phospholipids by the pathogenic antibodies, favoring activation of coagulation.
- HLA-DR4 and DRw53 were more frequently found in patients with APS.

By themselves the aPL may not be enough to cause thrombosis and may be the *first hit* followed by a *second hit* due to surgery/infection/autoimmune disease that may lead to the development of the syndrome.

CLINICAL MANIFESTATIONS

Antiphospholipid antibody syndrome is an important cause of acquired thrombophilia. Like other genetic prothrombotic factors, it does not have an *all or none* association with thrombosis. Risk of thrombosis is modified by many factors like aPL profile and persistence, associated autoimmune conditions and presence of other prothrombotic risk factors. Whereas LAC has been found to have strongest correlate with thrombosis out of the three prototype antibodies, association of antiβ2GP1 and aCA with thrombosis is far weaker and less well-understood. Triple antibody positivity confers the highest risk of thrombosis. Associated autoimmune conditions like SLE and prothrombotic risk factors like hypercholesterolemia, smoking and hypertension increase the risk of thrombosis. In SLE patients, LAC and isolated aCA positivity at medium to high titers have been found to increase the risk of thrombosis.

The common site of thrombosis is venous which can present as deep venous thrombosis, pulmonary thromboembolism or paradoxical thromboembolism through a patent foramen ovale. Arterial thrombosis commonly involves nervous system circulation causing stroke. Microcirculation can be involved commonly causing peripheral gangrene.

Besides thrombosis, many other clinical features may be associated with APS, though are not the defining features. These include chorea, seizures, cognitive dysfunction, and thrombocytopenia. Besides thrombosis in microcirculation, complement activation, release of various cytokines and direct neurotoxicity have been implicated in some of the neurological features. Livedo reticularis has been described as one of the important skin manifestations.

DIAGNOSIS

The importance of laboratory testing in establishing the diagnosis of APS needs no reiteration, since one half of the diagnosis rests on this. All good results depend on care taken in collecting the right sample at the right time, performing the right test in the right way and appropriate interpretation of the results. To this may be added the need for good quality control of the entire testing process. According to the current guidelines, laboratory testing includes testing for LAC (usually by a clot based test) and testing for aCA and aβ_2GP1 by serological methods.

Sample
Peripheral blood from a clean venepuncture is aliquoted into the following two parts:

1. 3.2% sodium citrate (9 parts blood:1 part citrate) for the LAC. The collection should neither exceed the mark for filling, nor should the tube be underfilled. The tube should be gently inverted 6 times and dispatched to the laboratory only after visual inspection confirms that the blood is free flowing and not clotted. This sample is processed the same way as a sample for routine coagulation testing except that it is important to make the plasma platelet free (less than 10,000 platelets/μL) by double centrifugation. This is because the platelets are a rich source of phospholipid and release this when the sample is thawed. This platelet phospholipid may then neutralize the antiphospholipid antibody and lead to a false negative result. The plasma can be separated and stored at –70°C for batch testing at a later date.

2. 1 mL of blood in a plain tube/red top collection tube. This sample is allowed to clot in the laboratory. The serum is separated and used for testing for aCA and aβ_2GP1.

Drawing samples from indwelling lines is best avoided, since presence of heparin used to flush the lines can affect the LAC. In very small children, if the sample collection is done using a butterfly needle, 6 times the volume of the blood in the tube need to be discarded, before collecting the sample in sodium citrate. Care must be taken to ensure constant mixing by gentle rotation of the collection tube since the increased time to collect the requisite volume may lead to clotting/activation which may affect the test results. If the samples need to be transported to distant laboratories, it is advisable to send platelet free plasma and serum instead of whole blood.

Tests

A baseline screening coagulogram for prothrombin time (PT) and activated partial thromboplastin time (aPTT) is performed. The aPTT is usually prolonged. The inhibitor nature of the LAC is confirmed by failure of the prolonged clotting time to correct on addition of normal plasma.

Lupus Anticoagulant (LAC)

The recent guidelines recommend performing of at least 2 tests to rule out LAC with confidence. The recommended tests are any 2 of the following:

- Diluted Russel viper venom test (dRVVT)
- Silica clotting time (SCT)
- Activated partial thromboplastin time (APTT).

Each of these steps is performed in 2 parts. The first part of the test is the *screen* step. In this the reagent is made poor in phospholipid. Since the LAC antibody is directed against phospholipid, the clotting time of the above tests is prolonged if the sample contains LAC. In the second *confirm* step, the same reagent is added with the only change being the addition of additional phospholipid (incorporated commercially in the second reagent). Since LAC is phospholipid dependent, the clotting time should return to normal in the confirm test. For the dilute Russell's viper venom time (dRVVT) system, the ratio of screen: confirm time is calculated. If greater than 1.2, it indicates the presence of LAC. The dRVVT is a popular test because of the ease of automation and the test bypasses the effect of the factors in the intrinsic pathway prior to the conversion of factor X to Xa. The silica clotting time is akin to the aPTT and is easy to automate. The previously recommended kaolin clotting time (KCT), though sensitive, is now not recommended because of issues related to automating this test. Other tests, though not recommended universally, are the Textarin Ecarin time and the dilute PT. Using more than 2 tests for screening for LAC are not recommended in order to avoid false positivity. Testing for LAC is not recommended when the patient is on anticoagulant therapy. Monitoring international normalized ratio (INR) on patients with

LAC is problematic because the LAC may also prolong the PT in a nonuniform manner making dosage decisions difficult.

Tests for Anticardiolipin and aβ_2GP1 Antibodies

Testing for aCA and aβ_2GP1 antibodies is simpler, since there are fewer issues with handling serum. The usual format is enzyme-linked immunosorbent assay (ELISA) based wherein the antigen—phospholipid (cardiolipin) or protein (β_2GP1) is coated on to microtiter ELISA platelets. On incubation, the antibodies in the serum bind to the plate and can be detected by color development using suitable enzyme reactions. The ELISA may be adapted to screen, or even detect the specific isotype immunoglobulin G (IgG) or Immunoglobulin M (IgM) and can be quantitated against a reference standard. Despite the ease of performance, some of the challenges in ELISA testing are the absence of suitable universal reference standard material; and the need for setting up local normal pediatric reference ranges, since the aβ_2GP1 antibodies are deemed positive if the value lies beyond the 99th centile. Obtaining sufficient pediatric normal samples has ethical considerations and often laboratories are forced to report on adult reference ranges, without validating them on children. A positive test due to the IgA isotype of the antibodies may result in a positive screen, however, its significance is not yet clear. This necessitates the quantification step with IgG and IgM isotypes which increases the cost.

Testing for Other Antibodies

Antiprothrombin antibodies Special mention is made of testing for antiprothrombin antibodies. Though not truly *criteria* antibodies, testing for these are undertaken in patients with APS who bleed, the other cause of bleeding being thrombocytopenia. The prothrombin levels may be low and these patients may have a prolonged PT along with aPTT.

Antiannexin antibodies These antibodies are measured in cases with recurrent pregnancy loss.

All positive tests LAC, aCA and aβ_2GP1 need to be repeated after 12 weeks and within 5 years of the last positive test to establish APS, since transient antibody positivity is frequent. Repeat testing for aCA and aβ_2GP1 is not a problem; however in children with thrombosis, receiving anticoagulant therapy, testing for LAC is compromised. Since it is not clinically feasible to stop the anticoagulation, by true definition, the diagnosis of APS in these children gets deferred. Positivity for different antibodies at different times is also described.

TREATMENT

Treatment is directed at preventing recurrence of thrombosis in patients who are aPL positive. Heparin followed by oral vitamin K antagonist is the treatment of choice in any venous thrombo-embolic event. Duration of this therapy depends on site of venous thromboembolism, aPL profile and titer and whether venous thromboembolism was provoked or not. Pulmonary thrombo-embolism, high-risk aPL profile and presence of autoimmune conditions or associated prothrombotic condition warrant lifelong treatment. Duration can however be shortened in case of single antibody positivity and a provoked thromboembolism. INR of 2.0–3.0 should be achieved while on oral vitamin K antagonists. A strict control of associated prothrombotic risk factor like hypertension, hypercholesterolemia and smoking should be achieved irrespective of previous thrombosis.

Arterial thrombosis in aPL positive patients warrants an evaluation for source of thrombus (cardiac vs. peripheral). Vitamin K antagonists are usually preferred for secondary prevention with an aim to maintain INR between 2.0 and 3.0. Some clinicians add low-dose aspirin to this regimen or maintain INR above 3.0 in case

the patient is positive for all three antibodies or has had multiple episodes of arterial thromboembolism however this increases the risk of bleeding significantly.

PREVENTION

Primary prevention is directed at prevention of thrombotic events in a child who has been found to be positive for aPL antibodies. Naturally the need of primary prevention will depend on the risk of thrombosis. Chronic prophylaxis is recommended in high-risk patients, which includes SLE, patients with positivity for LAC, persistent medium/high titers of anticardiolipin antibodies, triple positivity for all the three antibodies, and/or associated cardiovascular risk factors like hypertension.

Systemic lupus erythematosus increases the risk of first time thrombosis by nearly 4 times in aPL positive patients in comparison to healthy aPL positive adults. Moreover presence of aPL is a predictor of organ damage and mortality in SLE patients. All SLE patients with positive LAC or isolated persistent aCA at medium–high titers should be started on low-dose aspirin and hydroxylchloroquine (HCQS) for primary prevention of thrombosis. HCQS has been shown to be effective in reducing direct flares, reducing cardiovascular risk factors and preventing thrombosis. Acute conditions like surgery, prolonged immobilization, and postpartum period carry a high-risk of thrombosis in patients who are aPL positive and hence need thromboprophylaxis with low molecular weight heparin.

MORE ON THIS TOPIC

Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunological features of 121 patients in an international registry. Pediatrics. 2008;122(5):e1100-7.

Bertero MT. Primary prevention in antiphospholipid antibody carriers. Lupus. 2012;21(7):751-4.

de Groot PG, Urbanus RT, Derksen RH. Pathophysiology of thrombotic APS: where do we stand? Lupus. 2012;21(7):704-7.

Devreese KM, Pierangeli SS, de Laat B, et al. Testing for antiphospholipid antibodies with solid phase assays: Recommendations from the sub-committee on lupus anticoagulant/phospholipid-dependent antibodies. J Thromb Haemost. 2014: doi: 10.1111/jth.12537. [Epub ahead of print]

Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.

Pengo V, Denas G, Banzato A, et al. Secondary prevention in thrombotic antiphospholipid syndrome. Lupus. 2012;21(7):734-5.

Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on lupus anticoagulant/antiphospholipid antibody of the scientific and standardisation committee of the International Society on Thrombosis and Haemostasis: J Thromb Haemost. 2009;7(10):1737-40.

Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. Lupus. 2011;20(2):206-18.

IN A NUTSHELL

1. Antiphospholipid antibody syndrome is an important cause of acquired thrombophilia.
2. The association of aPL antibodies with thrombosis is not *all or none* and is modified by aPL profile and titers, associated autoimmune conditions and coexistent prothrombotic conditions.
3. Triple positivity, LAC positivity and persistent positivity for aCA at medium to high titer define high-risk aPL profile.
4. Association with SLE increases the risk of thrombosis significantly.
5. Other prothrombotic risk factors like hypertension, smoking, hypercholesterolemia should be addressed while managing patients with aPL positivity.
6. All patients with venous thromboembolism and high-risk aPL profile or SLE should be on lifelong oral anticoagulants with an aim to maintain INR between 2.0 and 3.0.
7. Low-dose aspirin is recommended for primary prevention of thrombosis in all patients with high-risk aPL profile.
8. All SLE patients with positive LA or isolated persistent aCA at medium-high titers should be started on low-dose aspirin and hydroxylchloroquine (HCQS) for primary prevention of thrombosis.

Section 47 COMMON EYE ABNORMALITIES

Section Editor Kirti Singh

Chapter 47.1
Common Visual Problems
Kirti Singh

Global estimates of blind children are 1.5 million below age of 15 years, of which, 1.3 million reside in Asia and Africa. An additional 7 million children suffer from low vision. In developing countries scourges like malnutrition with vitamin A deficiency, harmful traditional eye remedies coupled with inaccessibility to skilled medical care and rehabilitation are responsible for this ignominious statistic. Mere figures are deceptive since childhood visual impairment causes more significant life-long burden of disability in terms of number of *blind years* as compared to adults. The sentence of a *lifetime of blindness* not only has an adverse effect on educational and subsequent employment opportunities but also severely hampers psychomotor, social, and emotional development.

It is important to note that 75% of childhood blindness is both preventable and/or curable with cost effective interventions. To pursue the goal of eradication of preventable blindness, childhood blindness has been accorded priority status in *Vision 2020—the Right to Sight*, a global initiative. Very young children, less than 5 years are at maximum risk of visual loss. This is also the age group where early diagnosis and immediate intervention is required for prevention of amblyopia.

VISUAL IMPAIRMENT

Visual impairment includes low vision as well as blindness.

Low Vision Visual acuity of less than 6/18, but equal to or better than 3/60, or a corresponding visual field loss to less than 20° in the better eye with best possible correction.

Blindness Visual acuity of less than 3/60, or a corresponding visual field loss to less than 10° in the better eye with best possible correction (ICD-10 visual impairment categories 1, 2, 3, 4 and 5).

Etiology

Refractive error remains the prime villain in causing avoidable and reversible blindness in children. It accounts for 70–95% of childhood visual impairment in Asian and Oriental races. Hyperopia afflicts virtually every neonate and declines gradually to reach minimal proportions in the preschool age group (13%, National Program for Control of Blindness Report). Myopia ranges from 4.5% to 10.5% with incidence increasing from 4.5% in preschool age to 10.5% at 9–13 years, coinciding with pubertal growth spurt echoing in elongation of eyeball. Multiple studies have thus reiterated the importance of visual screening of school children. Many studies have hinted at a causal role of increasing education demands with incidence of myopia. Other causes are corneal, lenticular, retinal, glaucomatous and congenital anomalies.

DEVELOPMENT OF THE EYE

Initial development of eye starts by 22 days (2 mm length), with an outgrowth, the *optic vesicle* on either side of the prosencephalon. This is derived from neuroectodermal germ layer. Lateral growth of optic vesicles impinges on overlying surface ectoderm and initiates a thickening of ectoderm (*lens placode*). This lens placode subsequently invaginates, forms a *lens vesicle* and gets disengaged from surface ectoderm on day 33 to become buried. Differential growth of optic cup margins encroach and engulf the sunken lens vesicle on all sides except inferiorly. This inferior deficiency extends till inferior optic stalk and forms the *choroidal/embryonic fissure.* Failure of closure of inferonasally located fissure results in typical inferonasal coloboma of the eye **(Fig. 1)**. In inferior part of optic cup through the open embryonic fissure the mesenchyme condenses to form *hyaloid artery.* Mesenchyme surrounding neural tube condenses to form meninges which extend over optic vesicle. This mesenchyme differentiates into outer fibrous layer (dura mater) and inner vascular layer (pia and arachnoid) which cover the optic nerve. This elevates the status of optic nerve from being a mere cranial nerve to an outgrowth of brain tissue with proper coverings of the three meningeal layers.

Layers of Eye (Retina/Choroid/Sclera/Cornea)

Optic cup further differentiates anteriorly into outer fibrous layer (cornea) and inner vascular layer (iridopupillary membrane and iris). Posterior part of cup differentiates into an outer fibrous layer (sclera) and inner vascular layer (choroid and ciliary body). Retina is derived from two layers of optic cup with the inner layer forming neural part (rods, cones, bipolar, ganglion cells) and outer layer forming the retinal pigment epithelium (RPE) posteriorly and pigmented epithelium of ciliary body anteriorly. Thus, a potential space (obliterated space between two layers of optic cup) always exists between neural retina and RPE which is where a retinal detachment occurs. Optic nerve myelination proceeds from brain towards lamina cribrosa until just before birth, before it stops.

Lens

Primary fibers from lens placode form innermost *embryonic nucleus* till third month of fetal life. Secondary lens fibers are laid down concentrically in laminated layers by anterior epithelium/equatorial cells, which remain active throughout life. The *fetal nucleus* forms by 3–8 months, *infantile nucleus* forms in last weeks of fetal life till puberty. *Adult nucleus* starts forming after puberty. Thus, cataract at fetal nucleus or embryonic nucleus echoes the insult to growing fetus at the respective gestational age.
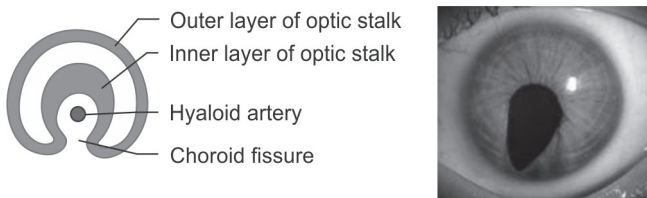
Figure 1 Typical iris coloboma is inferonasal due to failure of embryonic fissure to close

Outer layer of optic stalk
Inner layer of optic stalk
Hyaloid artery
Choroid fissure

Table 1 Stages of ocular development in utero

Stage	Development
2.6 mm (3 weeks)	Cephalic end of forebrain → optic pits
3.5 mm (4 weeks)	Optic vesicle invaginates
5.5–6 mm	Embryonic fissure
10 mm (6 weeks)	Lens vesicle and retinal layer differentiates
20 mm (9 weeks)	Cornea, sclera, and extraocular muscles differentiate
25 mm (10 weeks)	Optic nerve lumen obliterates
50 mm (3 months)	Optic tracts complete, retina growth
60 mm (4 months)	Hyaloid vessels atrophy
8th month	Fetal nucleus complete, retina layers all present, macula differentiates
9th month	Retina development (sans macula) complete Infantile nucleus appears, pupillary membrane disappears

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BOX 1 Visual development after birth

- *Six to eight weeks*: Eye contact, preferential looking at brightly colored/patterned objects or mother, social smile
- *Two months*: Protective blink reflex, any crossed eye (eso/exo deviations) straightens out by this time
- *Three to four months*: Hand eye coordination develops, starts to reach out for things, nonjerky eye movements, converges on near object and follows moving objects
- *Five months*: Gross color differentiation, stereopsis and binocularity start establishing
- *Six months*: Reaches out and grasps toys, recognizes faces, full conjugate eye movements. Watches small rolling balls at 5 feet, macula starts differentiating and fixation becomes stable
- *Six to ten months*: Identifies picture books, plays games, imitates, distinguishes strangers, good hand eye coordination
- *One year*: Sustained visual interest for both distant and near objects, angle of anterior chamber differentiates fully
- *Two years*: Corneal diameter attains adult dimensions. Child points to pictures in books, imitates vertical or horizontal strokes. Letter matching possible, visual acuity can be assessed by picture/Cardiff charts. Stereoacuity reaches near adult level
- *Three years*: Draws crude circle, can color jigsaw puzzles
- *Four years*: Depth perception, reads and writes letters, letter matching tasks possible
- *Five years*: Colors pictures, writes capital letters and in cursive
- *Six years*: Reads texts.

Equality is a utopian concept, not every child is born equal and every child is not similar, so attainment of these milestones may occur at slightly different ages in different children.

The growing eyeballs are covered by the fused eyelids, which separate by 7 months of gestation. Failure in separation results in cryptophthalmos. Stages of ocular development related to gestational age are summarized in **Table 1**.

VISION DEVELOPMENT IN A CHILD

Visual abilities evolve in a child over the period of time with exponential growth occurring during the first year. The concept of nature and nurture is best illustrated in visual development of the child because type and timing of visual inputs (nurture) are as important as the innate ability of the eye to perform as a seeing organ (nature). The utilization of visual inputs by the brain thus becomes a learned skill. Children at birth are unable to fixate or shed tears. The journey to fixate, follow, develop binocularity and stereopsis is travelled by the infant till his/her adolescence. In order to understand poor vision, the pediatrician needs to be aware of visual milestones so that he/she knows what age is appropriate. These milestones are elaborated in **Box 1**.

COMMON EYE PROBLEMS

Red eye, pain in eye, watering eye, wobbly eye and eye with poor vision are some of the most common ocular symptoms and problems. **Flow charts 1 to 5** present an algorithmic approach to diagnosis of these issues. Additionally, the parents need to be aware of indications of poor vision in early years. A few indicators of an eye problem in child are listed below:

- *Excessive tearing:* This may indicate blocked tear ducts
- *Red or encrusted eye lids:* This could be a sign of an eye infection
- *Constant eye turning:* This may signal a problem with eye muscle control
- *Extreme sensitivity to light:* This may indicate an elevated pressure in the eye or keratitis
- *Appearance of a white pupil:* This may indicate the presence of an eye cancer or a cataract.

Parental alertness and pediatrician's knowledge coupled with an ophthalmologist-optometrist back-up team is required to pick up these visual deficits and treat them in time. A child with poor vision never complains as she does not know what normal vision is and *what you do not have you do not miss*.

STRATEGIES TO PREVENT BLINDNESS

- *Primary prevention:* Rubella vaccination, vitamin A supplementation, measles immunization, breastfeeding, teratogen avoidance in pregnancy, genetic counseling for familial diseases hygiene of birth canal.
- *Secondary prevention:* Early detection and referral, timely surgery for congenital cataract/glaucoma, retinopathy of prematurity screening and prevention, prescribe spectacles for refractive errors.
- *Tertiary prevention:* Maximize residual vision: limit disability, low vision services, social support and adequate schooling.

Flow chart 1 Approach to red eye/conjunctival congestion

Red eye/conjunctival congestion

- Pain-nil/mild
  - Focal congestion
    - • Subconjunctival hemorrhage*
    - • Foreign body**
    - • Pertussis
    - • Episcleritis
  - Diffuse congestion
    - Look for discharge
      - Absent
        - **Allergic** (Itching usually present)
      - Present
        - **Watery**
          - Itching + (Vernal catarrh)
          - No Itching (Viral coniunctivitis)
        - **Mucopurulent** Bacterial/chlamydial conjunctivitis
- Pain +
  - Evidence of trauma +
    - • Blunt/concussion
    - • Penetrating (other signs of trauma)
    - • Battered baby syndrome
    - • Chemical burns
  - No evidence of trauma
    - Discharge present
      - • Conjunctivitis@ (associated mild photophobia)
      - • Keratitis (vision loss, associated severe photophobia)
      - • Blepharitis
    - Discharge absent
      - • Uveitis (circumcorneal congestion, keratic precipitate, vision loss)
      - • Dry eye/Stevens Johnson syndrome

Subconjunctival hemorrhage: Common in infants due to increase in venous pressure of head and neck due to uterine contractions during a normal vaginal delivery.
***Foreign body*: Vertical streaks of fluorescein stain seen on cornea. Foreign body may cause diffuse forniceal congestion if present over a long period.
@*Neonatal conjunctivitis caused by Chlamydia*, presents within 1–2 weeks of age; Gonococcal presents within 2 days of birth with thick/frothy/purulent discharge and swollen lids; Streptococci/Staphylococci/*H. Influenzae* are other organisms implicated. Urgent treatment with systemic erythromycin required. Treatment of mother and father/sexual partner mandatory.

Co-contributor: Ankush Mutreja

Flow chart 2 Diagnosis of poor vision

Poor vision

- Infant
  - **Signs of suspicion**
    - • Nystagmus/Nystagmoid movements
    - • Oculodigital sign (poking of fingers into eye)
    - • Photophobia/leukocoria/lacrimation
    - • Squeezing of eyes
    - • Squinting
  - Proceed with refraction and detailed ophthalmic examination
- Preschool child (1–5 years)
  - **Signs of suspicion**
    - • Delay in visual milestones
    - • Unable to imitate/copy
    - • Blank facial expressions
    - • Watching TV at close distance
    - • Plays only with toys with sounds
    - • Night blindness
- School child
  - Involves performance of visual tasks of increasing complexity. Common age where poor vision is picked up
    - Refractive errors
    - Accommodative anomalies especially insufficiency
    - Media opacities Corneal/lens/vitreous/lid hemangioma
    - Retinal: Retinopathy of prematurity, retinoblastoma
    - Optic nerve
    - Central nervous system

Co-contributor: Ankush Mutreja

Flow chart 3 Approach to watery eye

Watery eye

Pseudoepiphora
Hyperlacrimation due to causes other than lacrimal drainage system obstruction

True epiphora
Obstruction of lacrimal drainage apparatus

Physiological
hungry or irritable child

Associated systemic feature (fever, lymphadenopathy)

Look for associated signs/symptoms

Look for associated signs/symptoms

• Viral fever
• Kawasaki disease
• Stevens-Johnson syndrome

Pain +

Blepharitis

Photophobia

Itching

Sticky eye, Discharge +

No discharge

• Conjunctivitis
• Keratitis
• Corneal abrasion
• Foreign body (conjunctival or corneal)

Trichiasis

• Uveitis
• Congenital glaucoma
• Corneal abrasion
• Foreign body
• Trauma

• Allergic
• Vernal catarrh

Punctal atresia

Canalicular atresia

Nasolacrimal duct obstruction

Lacrimal pump failure— atonic sac (rare)

Co-contributor: Ankush Mutreja

Flow chart 4 Approach to pain in the eye

Pain in eye

Usually a complaint of older children who can articulate pain

Acute

Intermittent

Chronic

Not related to eye: sinusitis, migraine

Red eye present

Red eye absent

Strabismus due to defect in fusion, e.g., exophoria

Visual activities (reading)

No association with visual activities

Optic neuritis

Tumors of eye

Lid swelling

Cranial nerve involvement: 3rd/4th nerve palsy

• Refractive errors
• Convergence insufficiency/ Strabismus (strain in maintaining binocularity)
• Anisometropia

• Conjunctivitis
• Keratitis/uveitis/ glaucoma (photophobia ++; light intolerance ++)

• Blepharitis
• Hordeolum externum (stye)

Red eye present
• Allergies
• Dry eyes

No red eye
• Attention seeking behavior
• Parental attention
• Hysteria

Co-contributor: Ankush Mutreja

Flow chart 5 Child with Wobbly eye

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                        ┌─────────────────────┐
                        │  Child with Wobbly Eye │
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Nystagmoid
Initial pathological defoveating movement is a saccadic intrusion

Nystagmus
Rhythmic back and forth movements, initial movement slow

Not fixating
Wandering eye movements

Saccade
Fast conjugate eye movements occurring in burst with an interval

Flutes
Fast, small amplitude, horizontal movements without inter-saccadic interval

Opsoclonus
Multiplanar, large amplitude, fast conjugate saccadic movements

Physiological

Pathological

During initial stages of vision loss

Oscillation

Square wave
Movement off to one side and then back to fixation

Usually assumes nystagmoid action after some time

Back and forth across point of fixation

Jerky
Slow defoveating drift followed by fast refoveating connective saccadic movement

Pendular
Defoveating and foveating movements, both are slow

Mixed
Pendular in primary position and jerk in lateral gaze

Co-contributor: Ankush Mutreja

MORE ON THIS TOPIC

He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern china. Invest Ophthalmol Vis Sci. 2004;45(3):793-9.

Kalikivayi V, Naduvilath TJ, Bansal AK, Dandona L. Visual impairment in school children in Southern India. Community Eye Care.1997;45:129-34.

National Program of Control of Blindness. A study on childhood blindness: Visual impairment and refractive errors in East Delhi. Report by Community Ophthalmology, RP Centre. New Delhi: AIIMS; 2001.

Rahi JS, Sripathi S, Gilbert CE, Foster A. Childhood blindness in India: Causes in 1318 blind school students in nine states. Eye.1995;9:545-50.

Resnikoff S1, Pascolini D, Etya'ale D. Global data on visual impairment in the year 2002. Bull World Health Organ.2004;82:844-51.

Titiyal JS, Pal N, Murthy GVS, et al. Causes and temporal trends of blindness and severe visual impairment in children in schools for the blind in North India. Br J Ophthalmol.2003;87:941-5.

Chapter 47.2
Congenital Anomalies
Karobi Lahiri Coutinho

A congenital eye anomaly may be the result of genetic abnormalities, the intrauterine (uterus) environment, errors of morphogenesis, infection, or a chromosomal abnormality. The outcome of these disorders depends on a complex interactions between the prenatal deficit and the postnatal environment, Mother's diet, vitamin intake, glucose levels prior to ovulation and conception have long-term effects on fetal growth. Congenital anomalies of the eye, classified according to their location are listed in **Table 1**. Important defects are described below:

ANOPHTHALMIA

There is absence of one or both eyes. It manifests with a small bony orbit, a constricted mucosal socket, short eyelids, reduced palpebral fissure and malar prominence **(Figs 1A and B)**. Genetic mutations, chromosomal abnormalities, and prenatal environment can all cause anophthalmia. Prenatal diagnosis is made by ultrasound at 20 weeks of gestation. Amniocentesis can only diagnose an-ophthalmia when there is a chromosomal abnormality. Postnatal diagnosis is made by MRI/CT. Anophthalmia is associated with trisomy 13, Lenz syndrome, Goldenhar-Gorlin syndrome and Waardenburg syndrome. Treatment is mainly cosmetic with a prosthetic eye. Initially conformers are fitted into the eye; these are changed every few weeks in the first 2 years of life, after which a painted prosthetic eye is fitted into the child's socket. Children need to be checked regularly to ensure appropriateness of fit and size. No treatment exists for regaining vision by developing a new eye. Risks include a higher chance of having glaucoma or a detached retina.

Congenital cystic eye (also known as *CCE* or cystic eyeball) is an extremely rare ocular malformation where the eye fails to develop correctly in utero and is replaced by benign, fluid-filled tissue. Treatment of CCE is usually by enucleation, followed by insertion of an ocular implant and prosthesis.

CRYPTOPHTHALMOS

This is a rare congenital anomaly in which the skin is continuous over the eyeball with absence of eyelids **(Fig. 2)**. It is classified into three types: complete, incomplete and abortive. Failure of eyelid separation can be associated with maldevelopment of the

Table 1 Congenital eye anomalies according to location

Location	Anomalies		
Supraorbital ridges	Prominent	Shallow	Absent
Eyebrows	Bushy	Synophrys	Medial flare
	Arched	Hypoplastic	Absent
Eyelids	Ptosis, unilateral	Fused	Notched
	Ptosis, bilateral	Hemangioma	
Eyelashes	Long	Curly	Hypoplastic
Inner canthi	Epicanthus, unilateral	Epicanthus, bilateral	Laterally displaced
Lacrimal ducts	Obstructed	Excess tearing	Decreased tearing
Eye muscles	Esotropia	Exotropia	
Eye movements	Nystagmus	Wandering	
Globes	Prominent	Myxedema	Microphthalmia
Sclerae	Blue	Telangiectasia	Scarred
Conjunctivae	Dermoid	Telangiectasia	
Cornea	Macrocornea	Microcornea	Keratoconus
Pupils	Irregular	Asymmetric	Unreactive
Iris	Coloboma	Speckled	Hypoplastic
Pressure	Glaucoma, unilateral	Glaucoma, bilateral	
Retina	Coloboma	Mass	No red reflex
	Dysplastic	Degeneration	Abnormal pigmentation
Optic nerve	Bulging	Hypoplastic	Atrophic
Refraction	Myopia	Hyperopia	Astigmatism
Lens	Cataract, unilateral	Cataract, bilateral	Dislocated

underlying cornea and microphthalmia. Cryptophthalmos usually occurs on both sides and occurs in association with other multiple malformations collectively referred to as Fraser syndrome.

MICROPHTHALMIA

Also referred to as microphthalmos, nanophthalmia or nanophthalmos, is a developmental disorder of the eye that literally means small eye **(Figs 3A and B)**. One or both eyes may be involved. Microphthalmia in newborns is sometimes associated with fetal alcohol syndrome or infections during pregnancy,
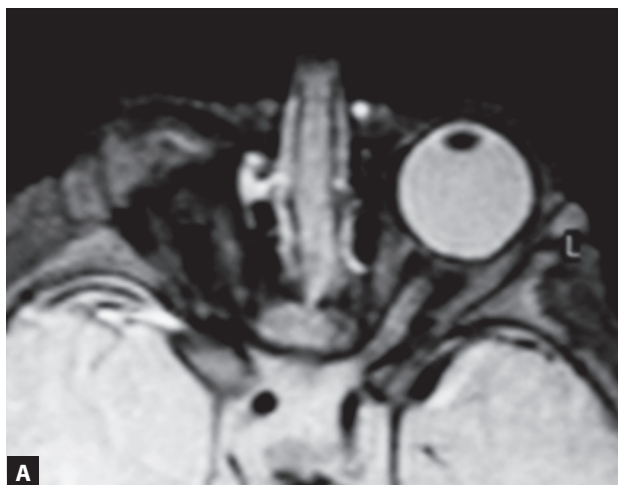
Figures 1A and B Anophthalmia

Figure 2 Cryptophthalmos

Figures 3A and B Microphthalmos

particularly herpes simplex virus, rubella and cytomegalovirus, but the evidence is inconclusive. Genetic causes of microphthalmia include chromosomal abnormalities [trisomy 13 (Patau syndrome), Triploid syndrome, and Wolf-Hirschhorn syndrome] or monogenetic Mendelian disorders. The latter may be autosomal dominant, autosomal recessive or X-linked.

COLOBOMA

A coloboma is a hole in one of the structures of the eye, such as the iris, retina, choroid, or optic disc. Present from birth, it is due to failure of choroidal fissure to close up completely before a child is born. The incidence of coloboma is estimated at around 0.5–0.7 per 10,000 births. A coloboma can be unilateral or bilateral. It can involve iris in which case the typical location is infero nasal coinciding with the location of embryonic fissure. This may be associated with coloboma of retina, optic nerve and lens zonules **(Figs 4A to D)**. The effects a coloboma has on the vision can be mild or more severe depending on the size and location of the gap. It may be associated with microphthalmia, glaucoma, nystagmus, scotoma, or strabismus. If retinal coloboma exists the vision is poor. Coloboma can be associated with a mutation in the *PAX2* gene.
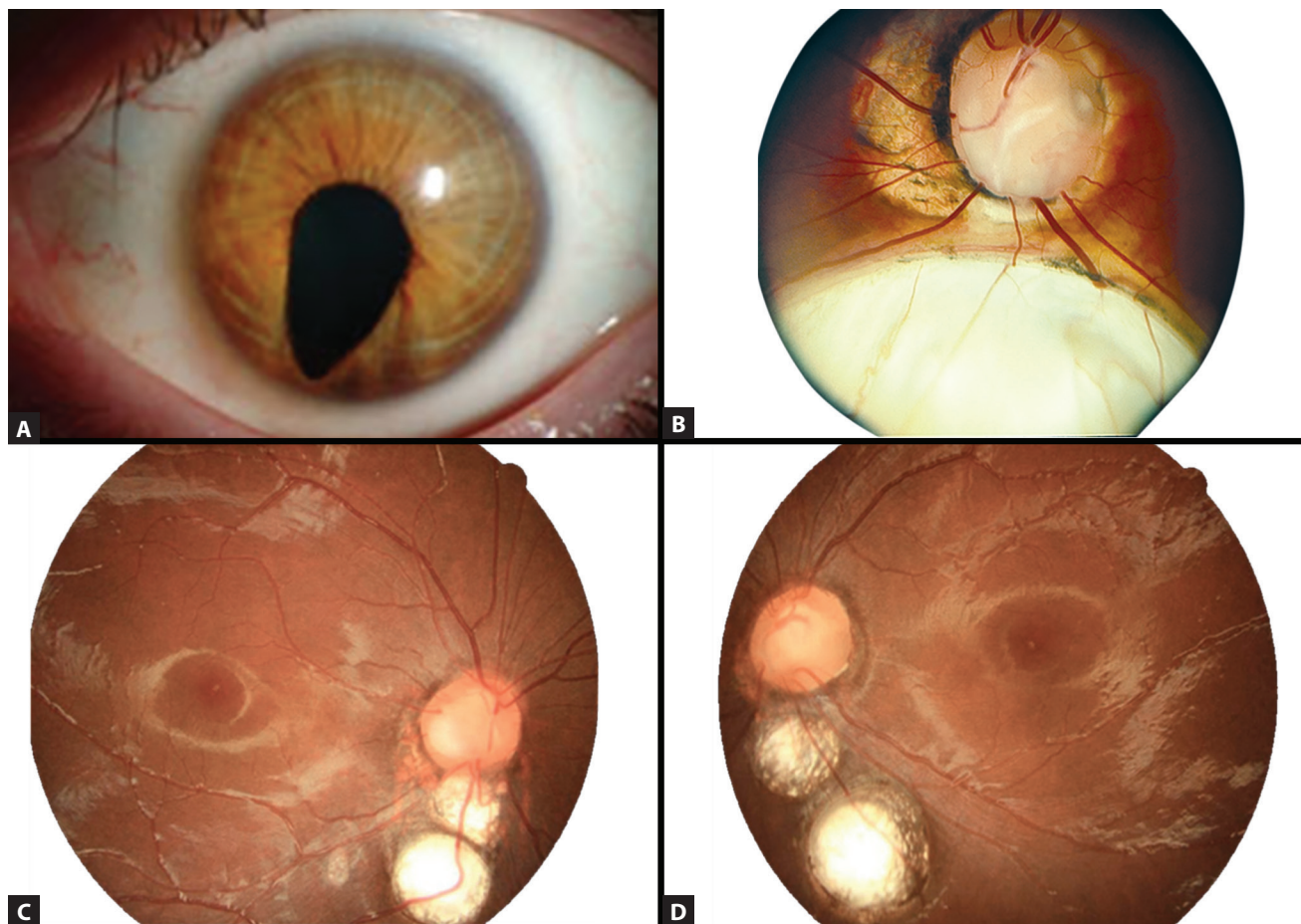
Figures 4A to D Coloboma of (A) Iris; (B) Choroid and optic nerve; (C and D) Retina
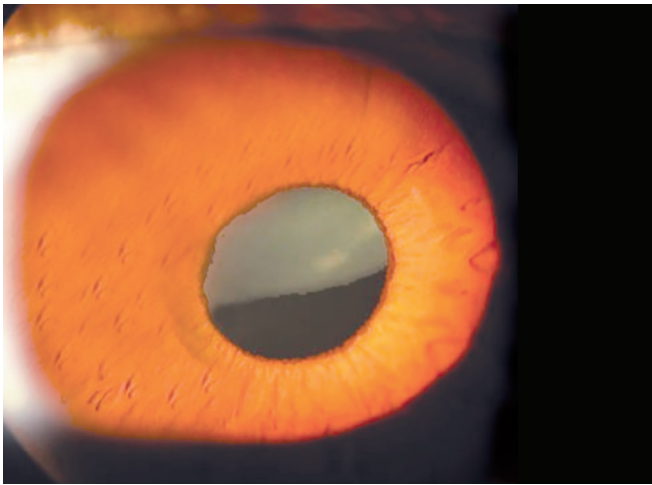
Figure 5 Congenital dislocation of lens

Figure 6 Cherry red spot

Other ocular malformations that include coloboma or are related to it include the CHARGE syndrome (coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genitourinary abnormalities, and ear abnormalities); Cat eye syndrome characterized by vertical colobomas caused by the deletion of short arm of human Chromosome 22, Patau syndrome; and Treacher Collins syndrome.

ANIRIDIA

It is the absence of the iris, usually involving both eyes. It can be congenital or caused by a penetrant injury. Vision may be severely compromised and the disorder is frequently associated with a number of ocular complications: nystagmus, amblyopia, buphthalmos, and cataract. The AN2 region of the short arm of chromosome 11 (11p13) includes the *PAX6* gene. Defects in the *PAX6* gene cause aniridia-like ocular defects. Aniridia may be broadly divided into hereditary and sporadic forms. Hereditary aniridia is usually transmitted as autosomal dominant or recessive manner (Gillespie syndrome). Sporadic aniridia mutations may affect the WT1 region adjacent to the AN2 aniridia region, causing Wilms tumor. These patients often also have genitourinary abnormalities and intellectual disability (WAGR syndrome). Isolated aniridia is associated with macular and optic nerve hypoplasia, cataract, and corneal changes.

APPROACH TO A CHILD WITH A CONGENITAL ANOMALY

The aim is to prevent heritable disorders by counseling the affected individuals or couples. Accurate genetic counseling starts with genetic evaluation that provides a unifying diagnosis which gives prognostic information and aids clinical management. Diagnosis is made by genotype or phenotype matching. Clues are provided by clinical findings, biochemistry and genetic analysis. Major anomalies including cataract and glaucoma and approach to their diagnosis and management are discussed elsewhere in this section. Other ocular disorders which can be a part of another
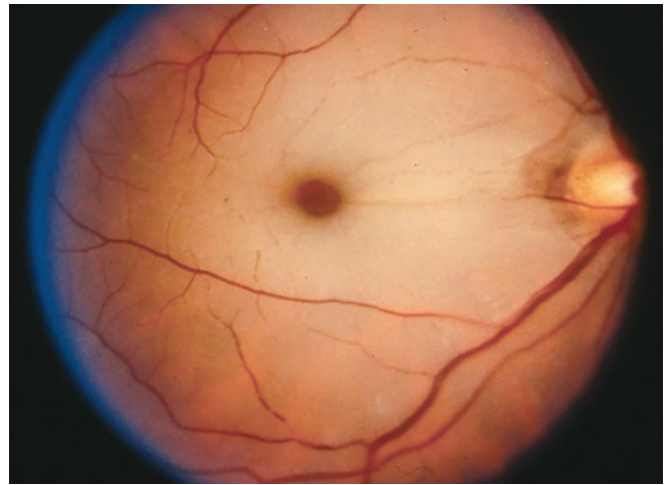
Figure 7 KF ring in Wilson disease

systematic illness are discussed with their respective disorders. A congenitally dislocated lens (in homocystinuria) is shown in **Figure 5**. A cherry red spot **(Fig. 6)** points to a diagnosis of Tay-Sachs disease, Niemann-Pick disease, Sandhoff disease, and sialidosis. Kayser Fleischer rings **(Fig. 7)** are diagnostic of Wilson disease.

MORE ON THIS TOPIC

Graham JW. Smith's Recognizable Patterns of Human Deformation. 3rd ed. Philadelphia: Saunders; 2007.

Lang K. Ophthalmology: A Pocket Textbook Atlas. 2nd ed. Germany: Thieme; 2007.

Pagon RA, Graham JM, Zonana J. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr. 2007;99:223-7.

Questions about Anophthalmia. From: www.anophthalmia.org. Accessed July 17, 2017.

Chapter 47.3
Refractive Errors
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Uncorrected refractive errors are the most common cause of visual morbidity in children. They can lead to permanent decrease in visual acuity, i.e., amblyopia, if timely intervention is not done. *Amblyopia*, also known as lazy eye, refers to decreased vision in a normal appearing eye due to abnormal visual processing from eye to brain in one eye. Blurred image projected on retina during the period of visual plasticity because of *ametropia* (refractive error when viewing distant objects) or *anisometropia* (two eyes have unequal refractive power; more than 2 diopters difference) can lead to development of suppression scotoma, amblyopia, and strabismus. Pediatricians being the first point of contact for these children should be alert in identifying the problem and refer in time to the ophthalmologist.

EPIDEMIOLOGY

Refractive errors account for half the cases of preventable vision impairment globally (153 million) and for 40% of preventable vision impairment in India. Prevalence of blindness because of uncorrected refractive errors is as high as 0.20% in India. Refractive error is one of the priority areas in Vision 2020 program, a global initiative to reduce blindness. Blindness due to this entirely benign correctable disorder is twice that of cataract in terms of blind years since it afflicts children. Uncorrected aphakia and amblyopia account for 5% blindness among children in blind schools in India. There is a definite link to racial and genetic factors with rapid urbanization contributing to increase in prevalence of myopia over the past few decades.

PATHOPHYSIOLOGY

Refraction is bending of light rays as they pass across a particular medium. Measured in diopters, it conveys the ability of the medium/ structure to focus parallel rays of light. Higher numerical value of diopters implies stronger focusing ability. The optical system of the eye comprises of cornea which accounts for two-third of refractive power of eye (40D) and lens which contributes the rest (20D). The lens can increase its refractive power by altering its shape by contraction of ciliary muscle by the process of accommodation. When cornea and lens in conjunction are able to focus light rays from infinity to retina, no refractive error (*emmetropia*) is present. If rays from infinity cannot be focused on the retina, *ametropia* or refractive error occurs.

To enable the eye to see an object, two mechanisms are required. Firstly *precise focusing* of light rays on retina is required. Secondly conversion of light impulse to electrochemical signals which are subsequently transmitted to occipital cortex by optic nerve via certain processing centers occurs. In refractive errors the first process is defective whereas in amblyopia the second process is defective. Refractive errors occur due to abnormalities in anatomy of refracting interfaces, absence of refractive structure or change in distance required for parallel rays for focusing (too long or too short an eye). These account for four main types of refractive errors: curvatural, index, axial and aphakia (absence of crystalline lens), respectively.

Most newborns are hypermetropic at birth and mild to moderate hyperopia (1–3 diopters) is the norm in infancy. This hyperopia which is due to a short eyeball tends to diminish over time coinciding with growth (enlargement) of eyeball in synchronization with corneal curvature to achieve emmetropia by 1–2 years of age. Disruption of this process of emmetropization causes myopia, hypermetropia or astigmatism. Refractive development is influenced by both environmental (nurture) and genetic (nature) factors, the debate of excessive near work being the cause or effect is still unresolved; however, many studies have implicated urbanization and excessive computer work as being responsible for the phenomenal increase in refractive errors in urban children versus rural children (4.1% of rural India versus 7.4% of urban India as per one study).

MYOPIA (NEAR SIGHTEDNESS)

Parallel light rays from distant objects are focused in front of the retina, whereas diverging rays from near objects focus on the retina without any requirement for accommodation. This error ensues as a consequence of a large globe (*axial myopia*) or increase curvature of refractive medium (steep cornea, *curvatural myopia*). The entity usually manifests in adolescence or early adulthood. Mild, simple or physiologic myopia is up to 3.0 D, moderate till 6.0 D and high-degree is greater than 6.0 D. Myopia usually progresses with age at a rate of 1 D/year to stabilize during adolescence. Higher rate of progression can be associated with pathological conditions such as keratoconus or glaucoma. High myopia or degenerative variety is often associated with degenerative changes in retina, choroid and optic nerve which cause poor vision despite spectacle correction. This myopia is associated with an increased risk of retinal detachment, macular degeneration, and cataract formation. Thus, children with this form of myopia require annual screening with dilated pupil examination to rule out these silent pathologies. Associations of myopia are prematurity, Marfan syndrome, Ehlers-Danlos syndrome and homocystinuria.

HYPERMETROPIA

It occurs as a result of image being focused posterior to or behind the retina giving rise to a blurred image on the macula. This is result of small globe (axial hyperopia) or flat cornea (curvatural hyperopia). Extreme hyperopia due to absence of lens as a refractive medium is called as aphakia. This is seen postcataract surgery when due to some complication or surgery done at a very young age, an intraocular lens could not be implanted. Mild hypermetropia is ubiquitous in babies and very young children, who outgrow it by 2–3 years. These long-sighted children can focus on distant objects, but require use of increased accommodative effort to view near objects. A child can overcome up to 10 D of hypermetropia by using his accommodation, therefore unless the error is high, visual acuity in hypermetropia remains normal.

The employment of excessive accommodative effort results in eyestrain and ocular fatigue over a period of time manifesting as frequent headaches. Since accommodation is neurally linked to convergence (near reflex), the excessive accommodation may cause inappropriate convergence leading to accommodative esotropia (convergent squint). This often presents at preschool age when the child is exposed to visual tasks of differing complexities. Proper correction of refractive error relieves accommodation, reduces convergence stimulus leading to correction of squint **(Figs 1A and B)**. Conditions associated with hypermetropia are corneal dystrophies, cataracts, microphthalmia and accommodative squint.

ASTIGMATISM

Astigmatism is a result of defocusing of rays in one direction due to variations in symmetry of corneal and rarely lenticular curvatures. Measured in cylinders (Dcyl), it is a common entity in children up to 3 years of age and resolves spontaneously by 3–5 years.
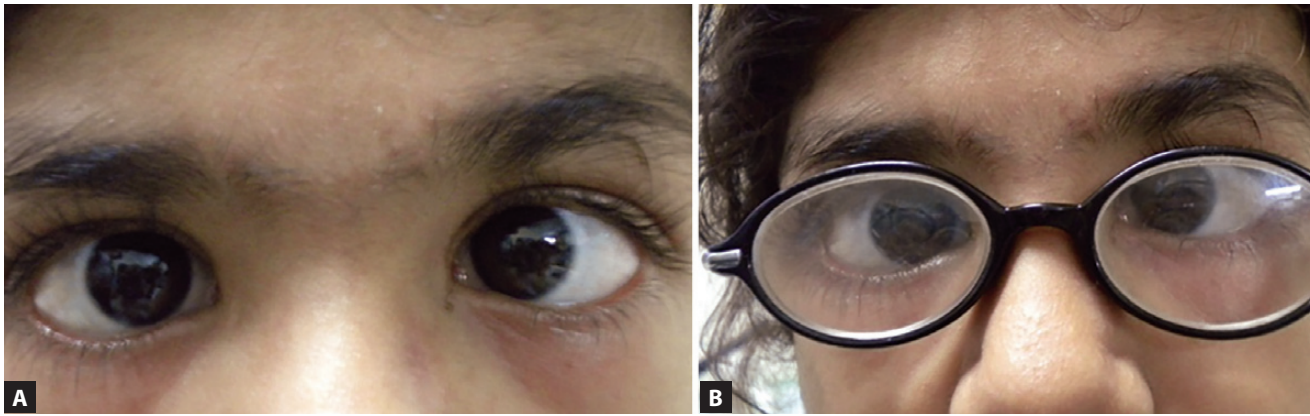
Figures 1A and B Esotropia in a young girl is partly corrected by wearing of a high plus spectacles

Cylindrical correction is required only for errors greater than 1.5 Dc. Astigmatism is of two types: regular and irregular, with the latter condition occurring due to corneal pathology like healed corneal scars or keratoconus. Uncorrected astigmatism of more than 3 Dc often leads to meridional amblyopia.

ANISOMETROPIA

It implies unequal refractive errors between both eyes. Large differences of more than or equal to 3.0 D with the most extreme form arising out of unilateral aphakia cause issues with binocularity by interfering with fusion of images of two eyes. Uncorrected anisometropia causes amblyopia where the eye with higher refractive error becomes lazy, due to nonestablishment of ocular dominance columns in lateral geniculate body and visual cortex of its side. Differing refractive states of two eyes result in different image sizes (aniseikonia) causing diplopia, headaches, photophobia, reading difficulties, nausea, dizziness and general fatigue. To avoid this, the plastic brain of child suppresses one image and amblyopia ensues.

WHEN TO SUSPECT REFRACTIVE ERROR?

The parent or caregiver gives history of difficulty in reading, distance viewing (blackboard, TV screen, school bus numbers), sitting very close to viewing object, e.g., TV screen, and holding books very close to face. *The child mostly does not complain as he/she is not aware of what normal vision is.*

These children squeeze their eyes to see distant objects by creating a pinhole effect and accommodate to see near objects in myopia and hypermetropia respectively **(Fig. 2A)**. The stressed eye manifests with frequent/recurrent headaches, itchy sore eyes causing frequent eye rubbing which causes recurrent stye or Hordeolum externum (due to dirty fingernails transmitting microbes to the eyelids). Thus, a child presenting with frequent styes/lid infections should have refraction done to rule out a refractive error **(Fig. 2B)**. As distant objects are blurred, these children avoid sports, and prefer reading pursuits thus earning the sobriquet of *bookworms*. Social interactions are hampered by their inability to recognize peers and activities taking place at a distance. This makes them adopt an introvert lifestyle.

Vision Screening

The pediatrician can check visual acuity with charts according to child's age. Each eye is tested separately for near and distance vision.

Preverbal Child (Infant/Toddlers)

Objective tests are required for this age group.
- Fixing and follow light/object.
- *Bruckner test (red reflex test):* Difference in intensity of binocular red reflex seen by direct ophthalmoscope, the eye with high error has paler reflex **(Figs 3A to C)**
- *Cover test:* A child with significant refractive error opposes, resists covering of better eye **(Figs 4A and B)**
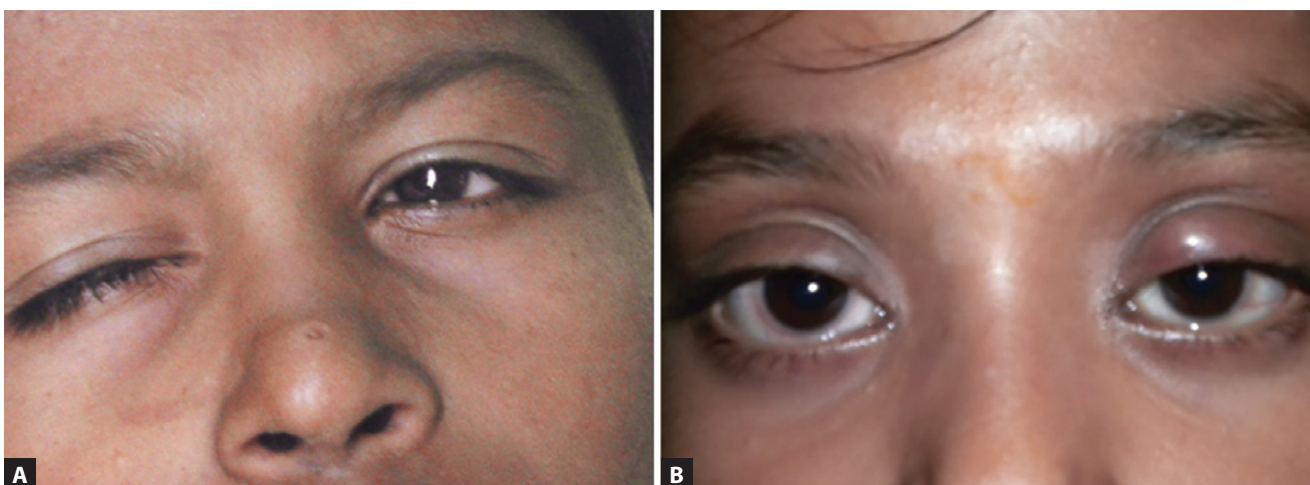
Figures 2A and B (A) Squeezing of right eye in a child with uncorrected hypermetropia on exposure to visual stimuli; (B) Hordeolum externum (stye) on left upper lid of an 8-year-old girl with undiagnosed myopia

Figures 3A to C Bruckner red reflex; (A and B) Left eye has white reflex, due to congenital cataract. Note the inward squinting of nonseeing left eye which has total cataract; (C) Red reflex showing after cataract in a child with implanted intraocular lens
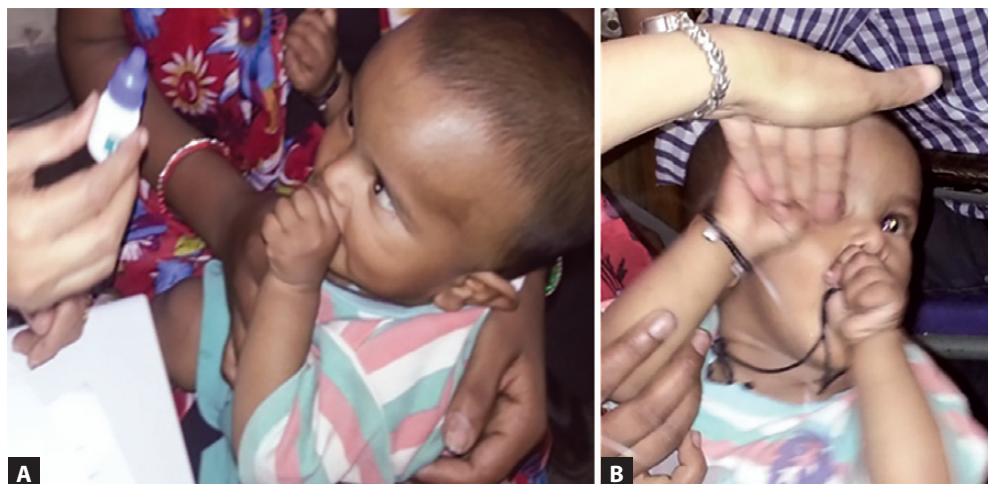
Figures 4A and B (A) The child is fixing at the colored top of a bottle; (B) On covering of right eye the child resists it and tries to force the examiner's hand away. This gives a clue that the left eye has poor vision

- Preferential looking tests (Tellers and Cardiff acuity charts) **(Figs 5 and 6)**
- Optokinetic drum **(Figs 5A and B)**
- Optokinetic nystagmus, pattern visual evoked potentials **(Figs 5A and B)**
- Early Treatment of Diabetic Retinopathy Study (ETDRS) charts with LEA symbols consists of four optotype (circle, square, apple, house) where the child is required to match target with similar shapes available on loose cards.

Verbal Child (School Going)

Standard ETDRS charts with geometric progression in each line with equal number of letters in each row are used **(Fig. 7A)**.

- *Snellen charts/Allen picture chart/Tumbling E or Landolt's chart* **(Figs 7B to D)**. American Academy of Pediatrics (AAP) recommends that a child aged 3–5 years should be able to read most of letters on 20/40 (6/12 Snellen equivalent) and children more than or equal to 6 years should read beyond 20/30 lines.
- Crowding of letters as present in Snellen or ETDRS chart decreases visual acuity in children suffering from amblyopia. Such children read better on single optotype chart (Single letter is shown in **Figure 7E**). The ETDRS charts have equal crowding of letters in each line versus Snellen and are more appropriate tests in amblyopia. In addition to vision evaluation, stereopsis should be evaluated to test for binocular function. Titmus fly test is a good screening test for testing stereopsis **(Figs 8A and B)**.
- Instrument-based screening by automated refractometer can also be done, to give an estimate of refractive error but preferred method is *wet refraction* which is performed on a child who

has been atropinized and is done using a retinoscope. The latter is an objective method, requiring minimal cooperation from child and is more reliable. This method is most reliable to confirm the presence or absence of a refractive error in a child.

School screening by teachers has to be done and if the child fails screening prompt referral to ophthalmologists for further management should be done. Screening for preschool children can detect refractive errors at an early stage.

Figures 5A and B (A) Tellers visual acuity chart; (B) Optokinetic nystagmus drum employs optokinetic nystagmus reflex where the eyes pursue moving bars in same direction followed by a quick saccade in opposite direction to fixate on next moving bar. Different sized stripes are used to quantify visual acuity

Figure 6 Tellers visual acuity chart viewing by a child. Gratings of varying cycles per centimeter against a gray background are presented and finest grating visible is the child's acuity. Concept is based on preferential viewing of patterns
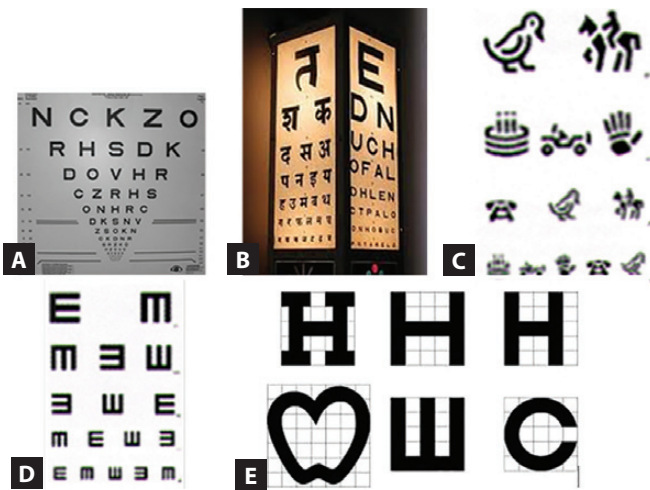
Figures 7A to E (A) ETDRS chart; (B) Illuminated Snellen's chart; (C) Allen picture chart; (D) *Landolt's E chart*; (E) *Single optotypes*

WHICH CHILD TO REFER TO OPHTHALMOLOGIST?

- Children with visual acuity of 6/9 or worse
- Difference in visual acuity between the eyes
- Child with strabismus/nystagmus
- Poor fixation and visual acuity assessment not possible.

The pediatrician should counsel parents that the child will have to undergo refraction under the effect of cycloplegic drops/ointment for children younger than 15 years of age and for children with squint at all ages. This is known as *Wet refraction*. Cycloplegia implies paralysis of ciliary muscle and sphincter pupillae with subsequent pupillary dilatation. The medication used is: atropine ointment 1% used TDS (three times a day) for 3 days for the complete effect to occur. It can be used BD (twice a day) for 3 days for children with light-colored eyes. The parents have to be informed that the child will be unable to read or do fine near work for 2–3 weeks postatropine usage. A postmydriatic test (PMT) is scheduled after 3 weeks. In view of this atropine refraction should not be performed during active academic activities of the child, instead it should be done during times of lean study period or vacations. The amount to be applied should be specifically and categorically instructed to be *less than a rice grain*, as excessive amount will be absorbed through nasal mucosa and cause atropine toxicity, signs of which are fever, cutaneous flushing of face, dryness of nose, tachycardia, disorientation and in extreme cases respiratory depression, and circulatory collapse.

The other medications which can be used are cyclopentolate 1% or homatropine 2%. The effect peaks in 60 minutes and lasts for 2–3 days. Tropicamide 1% is primarily a mydriatic with negligible cycloplegic effect (pure dilatation, no action on ciliary muscle) with peak effect occurring in 30 minutes and lasting for 6 hours **(Table 1)**. The child is advised not to play outdoor sports after application of these drops due to incapacitating photophobia (light intolerance).

Following wet refraction, the child is called after 3 weeks (atropine) or 3 days (Homatropine/cyclopentolate) for PMT for assessing final refractive correction under normal physiological pupil conditions. The final prescription for spectacles is given at that time. This rule is not adhered to in strabismus where the optometrist feels that the strabismus has components of accommodation. In that situation refractive correction is prescribed on the day of the wet refraction only, based on certain calculations.

Figures 8A and B Titmus fly test: Child wears polarized glasses, test images (housefly, animal, circle) are superimposed stereo pairs presented differently to each eye by the polarized filter. Form is visible as *standing out*/rising out of the page only with stereopsis. On monocular viewing or in a stereoblind child, test images appear in a flat field; (B) Gross stereopsis present; ability of child to pick out wings of the *fly in air* as shown

Table 1 Drugs used for refraction

Drug	Strength %	Dosage	Duration of cycloplegia	Indications	Adverse effects
Atropine ointment	1%	Thrice a day, for 3 days (rice grain size)	2–3 weeks	Infants/toddlers, associated esodeviation	Fever, flushing, drowsiness, tachycardia hypersensitivity (rare)
Cyclopentolate drops	0.5% (age < 1 year), 1% in older children	1 hour before retinoscopy, 4–5 instillations interval of 15 minutes	6–8 hours	Preschool children up to 7 years	Drowsiness, flushing less than atropine
Homatropine drops	2%	1 hour before instillation	3–4 days	Older children	

Hypermetropia of less than 3 D, myopia of less than 1 D, astigmatism of less than 0.5/0.75 Dc is not corrected except in children with associated squint, amblyopia, nystagmus or recurrent lid infection indicating asthenopia (eye strain). Such children need regular refractive checkup at 6 monthly intervals. **Tables 2 and 3** show appropriate refractive correction according to age.

Refractive errors can be effectively treated by appropriate correction. Spectacles, contact lenses and refractive surgery can be used depending on age, amount of refractive error, uniocularity and binocularity. Spectacles are most cost-effective and manageable option. The disadvantages of spectacles are induced prismatic effects and cosmetic blemish both of which are more commonly associated with higher refractive errors. The role of pediatrician is crucial in ensuring compliance with spectacle wear as the stigma associated with spectacles is a strong deterrent for the parents and child.

Treatment Options

Spectacle Correction
Figure 9 shows a ray diagram depicting focusing of light rays in uncorrected and corrected myopia/hyperopia.

Spectacle Type
Care should be taken while selecting size of spectacles so that child is not able to peep over the spectacles. Children should be prescribed plastic lens spectacles. Plastic is resistant to breakage by trauma sustained to the eye. Instead, on impact it shatters and pieces are contained inside the lens. This minimizes ocular damage due to glass shards of conventional spectacle lenses flying into the eye. Children in view of an active lifestyle incorporating physical activities are prone to facial injury and spectacle damage

Table 2 Correction of isometropia (similar refractive error in both eyes)

Age	Myopia	Hyperopia	Hyperopia with esodeviation	Astigmatism
< 1 year	−5 D or more	+6 D or more	+2.50 D or more	3 D or more
1–2 years	−4 D or more	+5 D or more	+2 D or more	2.5 D or more
> 2 years	−3 D or more	+4.5 D or more	+1.5 D or more	2 D or more

Table 3 Correction of anisometropia

Age	Myopia	Hyperopia	Astigmatism
< 1 year	−4 D or more	+2.5 D or more	+2.5 D or more
1–2 years	−3 D or more	+2 D or more	+2 D or more
> 2 years	−3 D or more	+1.5 D or more	+2 D or more
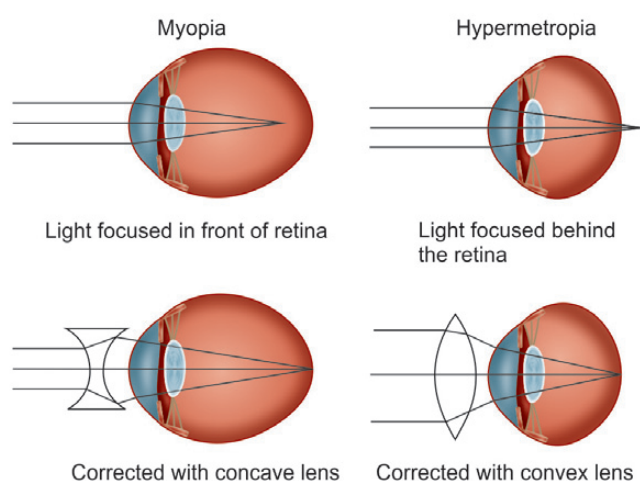
Figure 9 Ray diagram depicting focusing of light rays in uncorrected and corrected myopia/hyperopia. For astigmatism a cylindrical lens is used to *neutralize* the error

with subsequent ocular damage. Plastic in addition is light weight and less cumbersome to wear. However, plastic lenses are more expensive, lend themselves to scratches very easily and require frequent replacement. The spectacle frame needs to be sized according to child's intereye distance and requires change as the child grows older. Use of elastic band behind the spectacles can hold the specs snugly against the child's head and prevent dislodgement **(Figs 10A and B)**.

Contact Lenses
Contact lenses are reserved as an option for older children, primarily teenagers not compliant with spectacles due to social pressures. In young children they should only be resorted to in cases of unilateral aphakia (loss of crystalline lens) or anisometropia (difference in two eyes > 3–4 D) which hampers binocular fusion **(Figs 11A and B)**.

They score over spectacles in minimizing aniseikonia (unequal image size perceived by brain) and maintaining binocularity. They are a panacea for children involved in sport activities where spectacle handling can be difficult. These cosmetically acceptable devices for visual rehabilitation are easily used but hygiene measures need to be emphasized. Proper cleaning, handling and timely replacement prevents contact lenses-associated infections, allergies, etc.

Refractive Surgery
There are few reports of refractive surgery in unilateral high ametropia to improve binocularity, but it is not a widely accepted

Figures 10A and B Spectacles in a child and infant. The spectacle must totally cover the eye and be lightweight and with plastic lenses; (B) Infant with bilateral aphakia wearing light weight plastic frame and high plus spectacles of plastic lenses
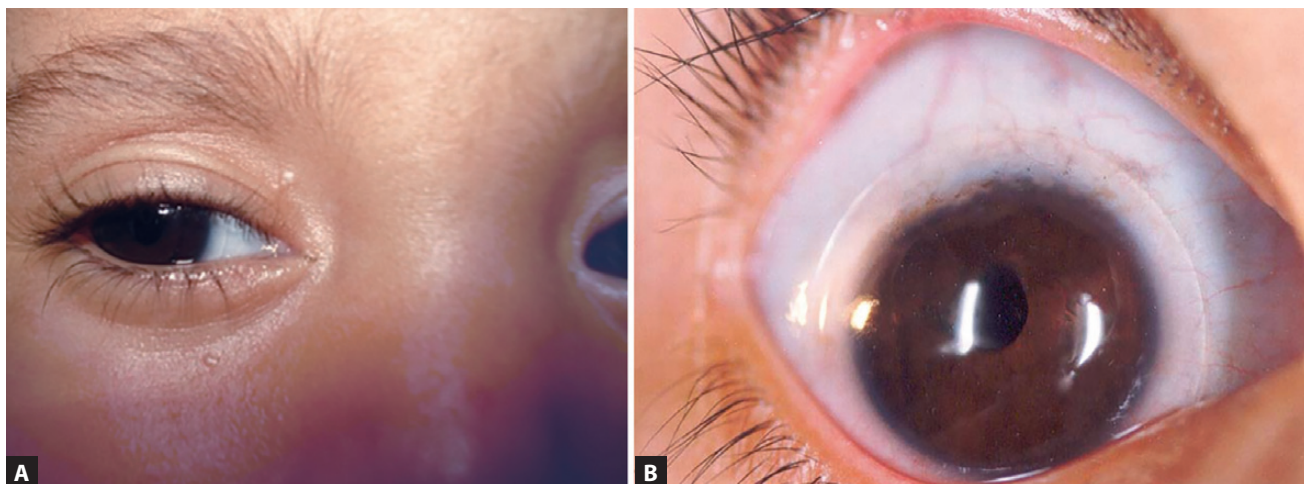
Figures 11A and B (A) One-year-old child wearing contact lens; (B) Close up view of a soft contact lens in an aphakic child
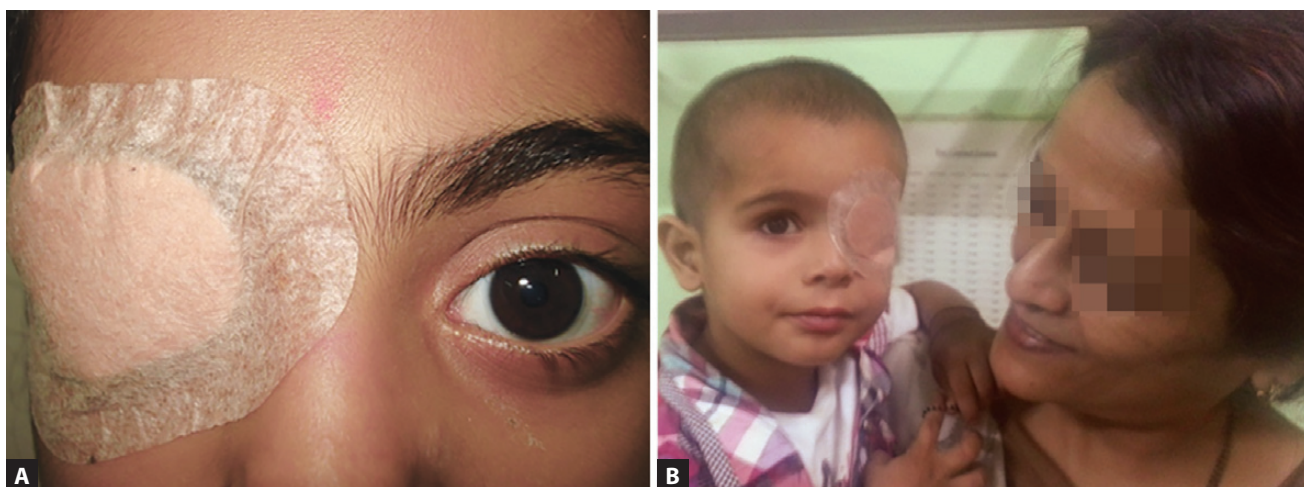
Figures 12A and B (A) Child with opticlude patch in position; (B) The child is comfortable with the patch on

procedure in children. Performance of any refractive surgery is deferred till child attains age greater than 18 years and the refractive error is stable for 2–3 years.

Additional Measures

Treatment of amblyopia involves occlusion of better eye to induce the worse eye to see. Patching with opticlude patch **(Figs 12A and B)** or Duane occluder with spectacle is used in a sequential manner. Full time or part time occlusion of better eye along with encouragement of children to use affected eye for near works like painting and homework helps in improvement of vision. Measures such as painting cartoons on the patches and motivation by means of prize of candy or treats improves compliance on part of the child. Regular follow-up is necessary in these patients to

Table 4 Recommended schedule for pediatric eye examination in refractive error

Age	Asymptomatic	At risk
Birth—24 months	6 months age	6 months of age or as required
2–5 years	3 years of age	3 years of age or as required
6–18 years	Before first grade and every 2 years thereafter	Annually or when required

monitor improvement and to prevent development of occlusion amblyopia in better eye. Penalization involves atropinization of better eye with appropriate correction of amblyopic eye.

Orthokeratology

An emerging technique, it utilizes specialized rigid contact lenses fitted overnight, to alter corneal shape in a controlled manner whereby myopia of –5 D can be reduced or ablated during daytime activities. This reversible process utilizes a programmed application of extremely high oxygen permeable lens material.

Risk factors requiring more frequent screening are prematurity, low birthweight, intraventricular hemorrhage, hydrocephalus, seizures, maternal infections during pregnancy, difficult or assisted labor, developmental delay, cerebral palsy, dysmorphic features and family history of retinoblastoma, congenital cataracts, metabolic or genetic disease. Treatment of refractive errors by spectacles is extremely simple, economical and feasible option. However, the stigma associated with spectacle use, ridicule of peers, restricted thinking of parents and elders has led to poor compliance of this treatment option. **Table 4** provides a recommended schedule for pediatric eye examination in a child detected with refractive error.

MORE ON THIS TOPIC

Cochrane GM, du Toit R, Le Mesurier RT. Management of refractive errors. BMJ. 2010;340:c1711.

Greenwald MJ. Refractive abnormalities in childhood. Pediatr Clin North Am. 2003;50:197-212.

Gwiazda J. Treatment options for myopia. Optom Vis Sci. 2009;86:624-8.

Naidoo KS, Jaggernath J. Uncorrected refractive errors. Indian J Ophthalmol. 2012;60:432-7.

Powell C, Wedner S, Richardson S. Screening for correctable visual acuity deficits in school-age children and adolescents. Cochrane Database Syst Rev. 2005;1:CD005023.

Sharma A, Congdon N, Patel M, Gilbert C. School-based approaches to the correction of refractive error in children. Surv Ophthalmol. 2012;57:272-83.

Song J, Al-Ghamdi I, Awad A. Pediatric refractive surgery in evolution. Middle East Afr J Ophthalmol. 2012;19:22-3.

Stephen P, Christiansen, Alex R, et al. Pediatric eye evaluations: I. Vision in primary care and community setting. II. Comprehensive ophthalmic examination. American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus panel. San Francisco: American Academy of Ophthalmology; 2012.

Taylor K, Powell C, Hatt SR, Stewart C. Interventions for unilateral and bilateral refractive amblyopia. Cochrane Database Syst Rev. 2012;4:CD005137.

Wojciechowski R. Nature and nurture: the complex genetics of myopia and refractive error. Clin Genet. 2011;79:301-20.

Chapter 47.4
Cornea and Conjunctiva
Ritu Arora, Aditi Manudhane

The cornea along with the conjunctiva, tear film, meibomian and lacrimal glands together constitutes the ocular surface. Dysfunction of any of these structures can result in low vision. Corneal diseases are a major cause of blindness worldwide, second only to cataract in overall importance. Almost 20% of childhood blindness is estimated to be caused by corneal blindness, with high regional variances from 2% to 50%. Corneal and ocular surface disorders in children can broadly be classified as developmental or acquired (infections, trauma, tumors, nutritional diseases, immune mediated, others).

DEVELOPMENTAL DISORDERS
Absence of the Cornea (Agenesis) and Cryptophthalmos
Cryptophthalmos is a congenital anomaly characterized by absence of lids, with the skin passing continuously over a malformed eyeball. It may be an accompanying feature of Fraser syndrome, an autosomal recessive (AR) disorder characterized by cryptophthalmos, cutaneous syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies.

Megalocornea
It is a rare congenital condition characterized by unilateral/bilateral, symmetric corneal enlargement. If the horizontal corneal diameter is more than 12 mm in the neonate or more than 13 mm in adult, megalocornea is present. Three patterns of megalocornea are: (1) Simple megalocornea; (2) Anterior megalophthalmos or X-linked megalocornea-associated with iris and angle anomalies, lens subluxation and cataract; and (3) Buphthalmos resulting from congenital glaucoma.

Keratoglobus
It is a bilateral generalized, noninflammatory thinning and anterior protrusion of the entire cornea from limbus to limbus. It is generally AR and may be a part of Ehlers Danlos syndrome.

Microcornea
In microcornea, corneal diameter measures usually 7–10 mm. This occurs as an isolated anomaly or associated with other anterior segment anomalies. In the latter situation it occurs with nanophthalmos or as a part of microphthalmos.

Congenital/Developmental Conditions Causing Corneal Opacities
These conditions are remembered by the mnemonic STUMPED and described below:
- **Sclerocornea (S)** is characterized by a peripheral white vascularized corneal rim that blends with the sclera and obliterates the limbus and scleral sulcus. Sclerocornea may be isolated or can be familial, inherited as an autosomal dominant (AD) trait.
- **Tears in Descemet's membrane (T):** Tears or breaks in Descemet's membrane may be caused by birth trauma or infantile glaucoma. Complicated forceps deliveries can result in periorbital ecchymosis and corneal edema. Slit lamp examination of the cornea reveals vertical refractile edges of the breaks in Descemet's membrane. The associated corneal edema gradually subsides leaving an essentially clear cornea with vertical striae. Corneal edema in infantile glaucoma is due to epithelial and stromal edema and is associated with an enlarged globe and photophobia. The tears in the Descemet's membrane in this condition are called as Haab's striae; they assume a random curvilinear distribution lying parallel to the limbus.
- **Ulcers (U)** in cornea are usually of infectious etiology and are dealt in detail later in the chapter.
- **Metabolic corneal opacities (M):** These may be the first clue to an underlying metabolic disorder. These disorders with corneal involvement are lysosomal storage diseases characterized by an abnormal accumulation of complex carbohydrates within keratocytes due to a deficiency of lysosomal enzymes **(Fig. 1)**.
  - *Systemic mucopolysaccharidosis Hurler syndrome (MPS IH)*: It is characterized by dwarfism, lumbar kyphosis and excess glycosaminoglycans in urine along with corneal clouding. Other disorders associated with corneal clouding include Scheie syndrome (MS I-S or MPSV) and Maroteaux-Lamy syndrome (MPS VIA and VIB). Exceptions are Hunter's syndrome and Morquio syndrome where corneal clouding occurs later in life. Sphingolipidoses-Fabry disease, caused by the absence of alpha galactosidase A, presents with whorl like opacity on the cornea. Hypertyrosinemia type II and cystinosis also show corneal involvement.
- **Posterior corneal defect (P):** There are four clinical groups of congenital posterior corneal defect:
  1. *Posterior keratoconus*: A posterior corneal depression with minimum overlying opacity.
  2. *Peter's anomaly*: A corneal opacity with iris strands adhering to its margins
  3. A corneal opacity with adherent iris strands and corneolenticular contact or cataract.
  4. Corneal staphyloma.
     Ultrasound biomicroscopy is extremely useful imaging modality to assess details of the anterior chamber in the presence of hazy cornea. Treatment of Peter's anomaly is penetrating keratoplasty, with guarded visual outcome. Mesenchymal dysgenesis of the anterior segment includes congenital anomalies of the iris and iridocorneal angle along with posterior corneal defects.
- **Corneal Endothelical dystrophies (E):** The corneal dystrophies (CD) exhibit diffuse cloudiness at birth and include: (1) Congenital hereditary endothelial dystrophy—this is AR or AD.
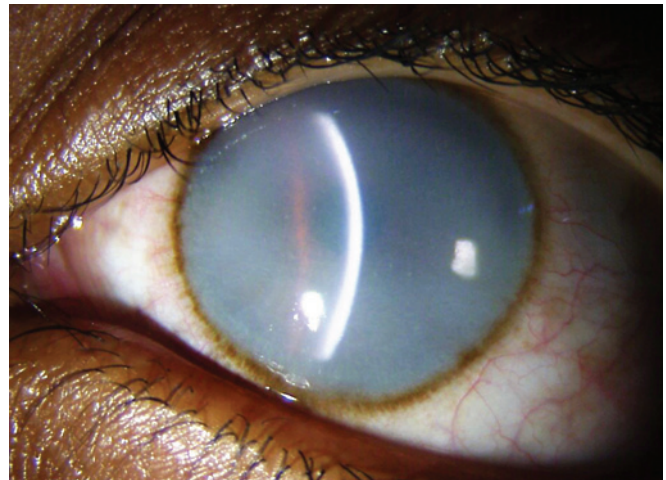
Figure 1 Diffuse corneal clouding in a patient of Hurler syndrome

The AR form appears at birth and is associated with profound corneal clouding along with nystagmus. The AD form appears by about 2 years of age, and has less severe corneal clouding. In the latter type child has tearing and light sensitivity without nystagmus; (2) Congenital hereditary stromal dystrophy; and (3) Posterior polymorphous dystrophy.

- **D**ermoid (D): Discussed on page 2581.

INFECTIONS

Infectious corneal disease is an important cause of blindness worldwide **(Fig. 2)**. Among children, amblyopia is the major concern, as altered corneal transparency due to keratitis prevents normal neurophysiological development. Incidence of blindness caused by keratitis in children is 20 times higher in tropical developing countries when compared to developed countries. Factors influencing this disparity are prevalence of low socioeconomic status, incomplete immunization profile and systemic diseases, including hypoxic encephalopathy, pulmonary stenosis, protein-energy malnutrition, multiple congenital anomalies and prematurity.

Ocular trauma is the most important predisposing factor for infectious keratitis in children. Other factors are chronic steroid use, secondary infections postexanthematous fever, ocular rosacea, previous ocular surgeries, congenital facial paralysis, previous herpetic infection, dry eye and eyelid abnormalities. *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* are among the common causative organisms.

Bacterial keratitis is characterized by intense suppuration, congestion, tearing and photophobia. The rapidly spreading infections lead to necrosis, ulceration, abscess formation and finally corneal perforation. Fungal keratitis often occurs following trauma with vegetable matter. In tropical climates filamentous fungi such as *Fusarium* and *Aspergillus* are the most common causative organisms. Signs in this type of keratitis are more severe than symptoms in the initial stages. Epithelium breakdown results in stromal ulceration and hypopyon, which may further lead to formation of descemetocele and corneal perforation. Characteristic satellite lesions may be seen peripheral to the focal area of infiltration.

Management

Treatment-based on culture and sensitivity testing is difficult as the rate of culture positivity is low. Empirical treatment consists of topical fluoroquinolones, fortified cefazolin 5% (to cover gram-positive organisms) and fortified tobramycin 1.4% (gram-negative

Figure 2 Corneal ulcer with hypopyon post-trauma
with vegetable matter

organisms). In cases where fungal infection is suspected topical 5% natamycin is started to cover the common filamentous fungi. Other antifungals that can be used include amphotericin B, voriconazole and itraconazole. Scleral involvement or endophthalmitis are the indications for systemic antibiotics.

Ocular Involvement in Exanthematous Fever

Keratoconjunctivitis may occur in patients suffering from viral infections such as herpes and measles. Ocular lesions on healing may result in scarring and blindness. Varicella may result in a mild conjunctivitis. Corneal thinning with ulceration may occur in generalized malnutrition and vitamin A deficiency in particular. These ulcers may get secondarily infected and may perforate resulting in the formation of staphyloma.

Neonatal conjunctivitis presents during the first month of life. It may be aseptic or septic. *Aseptic neonatal conjunctivitis* is a *chemical conjunctivitis* induced by instillation of silver nitrate solution, which is sometimes used for prophylaxis of infectious conjunctivitis. The incidence has decreased since erythromycin ointment replaced silver nitrate. Bacterial and viral infections are major causes of septic neonatal conjunctivitis, with *Chlamydia* being the most common infectious agent. Other agents include Herpes simplex and *N. gonorrhoea*. Infants may acquire these infective agents as they pass through the birth canal during the birth process.

NONINFECTIOUS CORNEAL INVOLVEMENT

Nutritional Disorders

Dietary deficiency of vitamin A most commonly affects the eyes, and it can lead to blindness. The term *Xerophthalmia* (from the Greek word *xeros,* meaning dry), covers all ocular manifestations resulting from vitamin A deficiency. Features may range from Bitot's spot to conjunctival and corneal xeroses to corneal ulceration. The serious eye manifestations of vitamin A deficiency leading to corneal destruction and blindness, i.e, aseptic corneal melt is known as keratomalacia. Clinical manifestations, management and prophylaxis are described in detail in Chapter on Vitamin A Deficiency in Section 22 on Nutritional Disorders.

Trauma

Ocular trauma in children can occur by blunt force, projectile injuries, penetrating injuries with sharp objects, chemical exposure and burns, explosion type injuries and crush injuries. Common causes of blunt trauma are *Gilli danda* (a sport involving wooden stick hitting a small polished wooden cylinder, popular in India), fire cracker injury and cricket ball injury. These present with a wide variety of injuries from periocular soft tissue hematomas, lid lacerations, corneal abrasions, traumatic iritis to orbital wall fractures. Projectile trauma represents the effect of a moving object transferring its kinetic energy to the periocular tissue. The damage caused depends upon the size, velocity and the impact vector. This ranges from a corneal abrasion to hyphema, orbital fracture to a ruptured globe. Chemical injuries, particularly alkali burns are among the most devastating type of eye trauma **(Fig. 3)**. Injuries and their management are discussed separately in Chapter 47.10 further in this section.

Shaken (Battered) Baby Syndrome

This is widely recognized as one of the most important forms of child abuse. Victims are mostly under 3 years of age. Clinical findings in affected infants include subdural/subarachnoid hemorrhage, intraretinal/vitreous hemorrhages, hypoxic-ischemic brain injury and fractures at various stages of healing and cutaneous injuries.
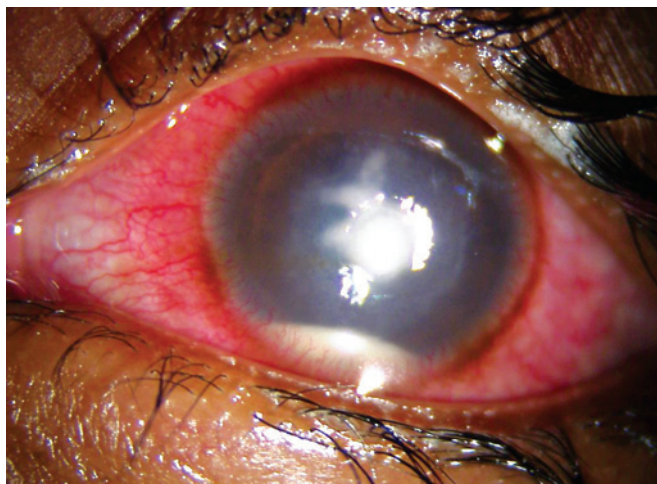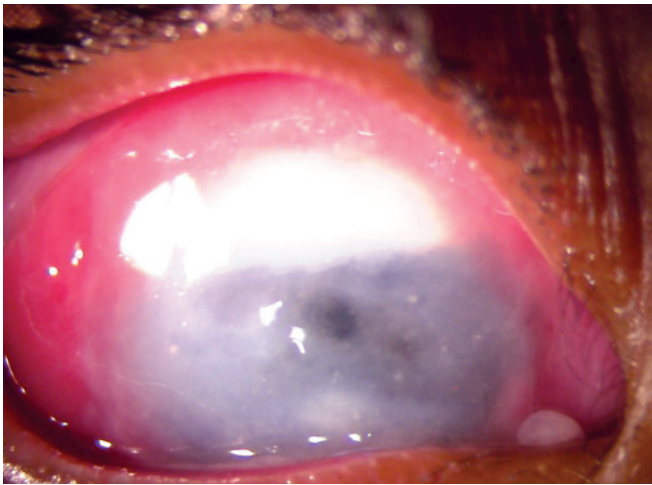
Figure 3 Acute chemical injury with intracorneal lime particles

Tumors

Nonmalignant tumors of the ocular surface include dermoids and dermolipomas.

Dermoid **(Fig. 4)** They are benign congenital tumors containing ectopic tissues, most commonly found in the inferotemporal quadrant at the corneal limbus. They may present as an isolated finding or commonly as a part of Goldenhar or Franceschetti syndrome (discussed later).

Epibulbar dermoid are benign developmental choristomas (normal tissues in abnormal location), derived from displacement of ectoderm to a subcutaneous location. These lesions are located in regions of the bulbar conjunctiva, limbus, cornea, and/or caruncles. Lined by keratinized stratified squamous epithelium with a fibrous wall, they contain dermal appendages such as sweat/sebaceous gland and/or hair follicles **(Fig. 4)**.

Limbal dermoids are most commonly located in inferotemporal quadrant along the limbus. They may be associated with syndromes such as ring dermoid syndrome with conjunctival extension, preauricular tags, palpebral coloboma, Goldenhar syndrome (preauricular fistulae, preauricular appendages, and epibulbar dermoids or lipodermoids), and mandibulofacial dysostosis of Franceschetti syndrome.

Dermolipomas are mostly congenital but may remain unnoticed until adulthood. They are more commonly found in the
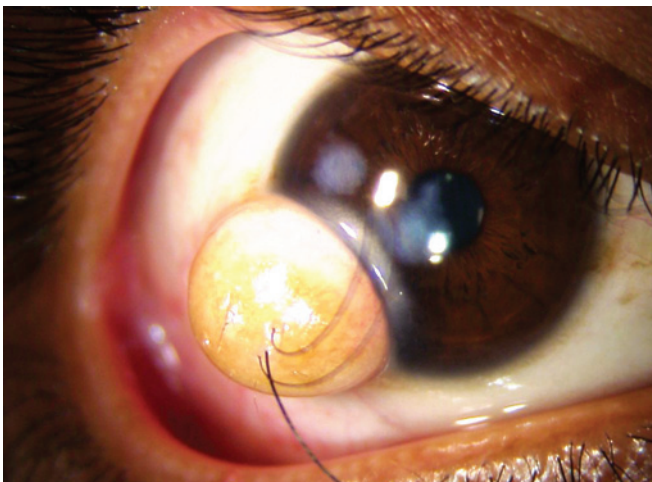
Figure 4 Limbal dermoid in a patient of Goldenhar syndrome. Note the hair growing out of the dermoid

superotemporal conjunctival fornix extending to the lacrimal gland and/or orbit posteriorly and may reach limbus anteriorly thereby making it difficult to clinically judge its posterior extent. Histologically they are lined by conjunctival epithelium and the subepithelial tissue contains adipose tissue admixed with collagenous tissue.

Treatment

Small limbal dermoids are managed conservatively. Flattening of the cornea along the axis of the lesion results in astigmatism. Refractive correction must be prescribed to prevent amblyopia. Larger or symptomatic dermoids can be approached by lamellar sclerokeratectomy with primary closure or amniotic membrane transplantation with corneal graft if the defect is deep or full thickness. Majority of dermolipomas do not require treatment. The larger or cosmetically unappealing ones can be managed by excision of the entire orbitoconjunctival lesion through a conjunctival forniceal approach.

Corneal Keloid

Keloids are reactive fibrous tissue proliferations occurring secondary to a vigorous fibrotic response to corneal perforation or injury. Corneal keloids are seen as white, protuberant, glistening masses which involve cornea and anterior segment or even replace the entire cornea. Diagnosis is confirmed by a corneal biopsy. Rarely congenital corneal keloids may be seen in association with other anomalies like peripheral iridocorneal adhesions, anterior segment mesenchymal dysgenesis, aniridia and cataract with anophthalmia. They have been described in children with Lowe syndrome, Rubinstein-Taybi syndrome, and fibrodysplasia ossificans progressiva. Management options include simple excision, lamellar keratoplasty and penetrating keratoplasty.

Epithelial Conjunctival Tumors

Several benign and malignant tumors can arise from squamous epithelium of the conjunctiva:

- *Papilloma:* This appears as a pink fibrovascular frond of tissue arranged in a sessile or pedunculated configuration. This benign tumor is often associated with human papilloma virus (subtypes 6, 11, 16 and 18). It may regress spontaneously or may require cryotherapy followed by excision. Topical mitomycin C and interferons can be used.
- *Hereditary benign intraepithelial dyskeratosis:* A rare benign autosomal-dominant condition seen amongst Caucasian, African-American and American-Indians (Haliwa Indians). It is characterized by bilateral elevated fleshy plaques on nasal or temporal perilimbal conjunctiva and buccal mucosa. Small lesions are managed using lubricants and corticosteroids with surgery being reserved for larger lesions.

Squamous Cell Carcinoma/ Conjunctival Intraepithelial Neoplasia

These malignant tumors of surface epithelial cells occur more commonly in immunocompromised patients and those with underlying DNA repair abnormalities such as xeroderma pigmentosum **(Figs 5 and 6)**. In intraepithelial neoplasia, anaplastic cells are confined to epithelium whereas squamous cell carcinoma displays extension of anaplastic cells through basement membrane into the conjunctival stroma. Management varies with the extent of the lesion. Tumors in limbal area require alcohol epitheliectomy for the corneal component and partial lamellar sclera-conjunctivectomy with wide margins for conjunctival component followed by freeze-thaw cryotherapy to remaining adjacent bulbar conjunctiva. Extensive and recurrent tumors require adjuvant topical mitomycin-C, 5-fluorouracil or interferon.

Figure 5 Ocular surface squamous neoplasia at the limbus with feeder vessels

Figure 6 Xeroderma pigmentosa with dry eye

Immune-Mediated Disorders

Steven Johnson Syndrome

Steven Johnson syndrome and its more severe form, toxic epidermal necrolysis (TEN) are autoimmune disorders of skin and mucous membranes occurring postexposure to certain drugs such as sulfonamides, phenytoin or nonsteroidal anti-inflammatory drugs and rarely due to infections such as Herpes simplex or mycoplasma pneumonia. The acute phase occurs 1–3 weeks after exposure to the triggering agent and is characterized by a systemic prodrome followed by mucous membrane and skin lesions. Ocular findings in the acute phase include intense *membranous conjunctivitis* and may develop a *secondary infectious bacterial conjunctivitis*. The raw conjunctival surfaces may adhere leading to formation of symblepharon. Cornea may show persistent epithelial defects and pannus formation. The chronic stage is characterized by dry eye, lid involvement with entropion, ectropion, trichiasis and damage to meibomian glands. Keratinization of the lid margins and palpebral conjunctiva causes corneal damage via blink-related microtrauma to the corneal epithelium. The loss of limbal stem cells results in conjunctivalization of corneal surface **(Fig. 7)** with resultant severe visual loss. Management depends on stage of the disease process. In acute stage, the ocular surface is protected with intensive lubricants, anti-inflammatory agents and topical antibiotics. Early symblepharon formation is prevented by mechanical lysis of the symblepharon. During chronic phase dry eye is managed intensively and eyelid abnormalities treated. Limbal transplant is performed for significant limbal stem cell deficiency.

Staphylococcal scalded skin syndrome is a TEN like entity occurring in children, most commonly precipitated by a staphylococcal infection. It results due to an exotoxin produced by *Staphylococcus aureus*. Ocular findings are similar but milder to erythema multiforme major. Mucopurulent conjunctivitis or membranous conjunctivitis with scarring may occur. Aggressive antibiotic therapy is started early. A skin biopsy helps to distinguish between staphylococcal form and TEN.

Vernal Keratoconjunctivitis

This is a bilateral, allergic disease characterized by itching, a white ropy discharge and seasonal variation. The most common underlying cause being Type 1 hypersensitivity reaction since positive family history of allergy is ubiquitous. Some consider it to be a type 4 hypersensitivity reaction.

Patients present with symptoms of profound itching, excessive tearing, mucous production, photophobia, burning or foreign body sensation. The upper tarsal conjunctiva shows variable sized papillae. Large flat topped cobblestone papillae may be

Figure 7 Conjunctivalization of cornea in a patient of Steven Johnson syndrome with severe dry eye

seen causing mechanical ptosis **(Fig. 8)**. Thick tenacious mucus strands are found in the fornix along with inflammation of the bulbar conjunctiva. Corneal involvement varies from superficial punctuate keratopathy to large epithelial defects. Deposition of fibrin and mucous on de-epithelialized surface result in plaque formation and a shield ulcer **(Fig. 9)**. Untreated it can result in secondary infection, stromal ulceration and corneal scarring.

In tropical countries, limbal form of disease predominates. This is characterized by presence of large conjunctival papillae at corneoscleral limbus, as a consequence of which superficial vascularized pannus may form. Collections of inflammatory cells rich in eosinophils, present at apices of limbal papillae form Horner-Trantas dots.

Vernal keratoconjunctivitis is a self-limiting disease associated with sight-threatening complications. Management aims at control of symptoms and to limit development of vision-threatening complications.

Topical antihistamines and mast cell stabilizers are the mainstay of treatment. Mast cell stabilizers currently in use are 4% sodium cromoglycate, 0.1% lodoxamide and 2% nedocromil sodium. Topical steroid therapy is used initially for control of acute inflammation. Long-term steroid therapy is avoided due to concerns regarding elevation of intraocular pressure or cataract formation. Only diluted steroids may be considered for long-term in refractory cases.

Topical cyclosporine 2% and tacrolimus are newer drugs being used in the management of vernal keratoconjunctivitis.
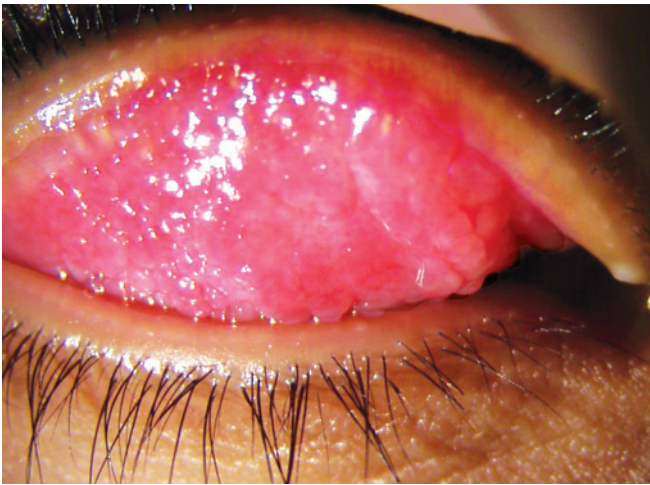
Figure 8 Cobblestone papillae in severe vernal keratoconjunctivitis
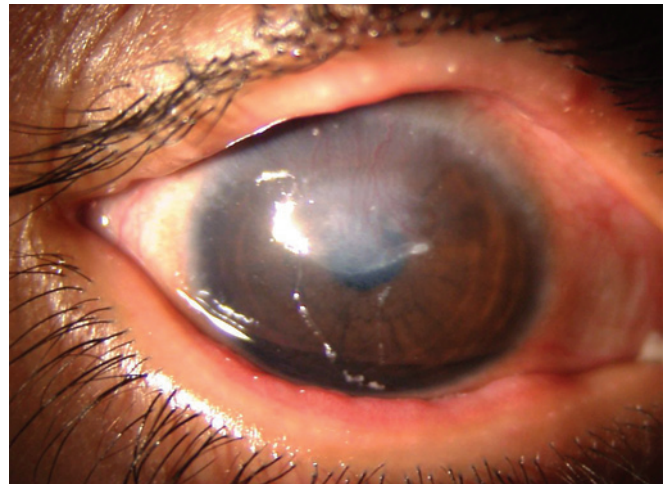
Figure 9 Shield ulcer in active vernal keratoconjunctivitis
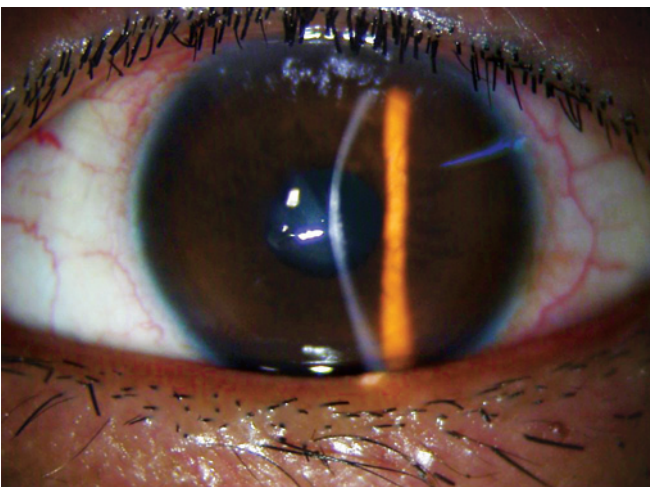
Figure 10 Advanced keratoconus with healed hydrops and scarring
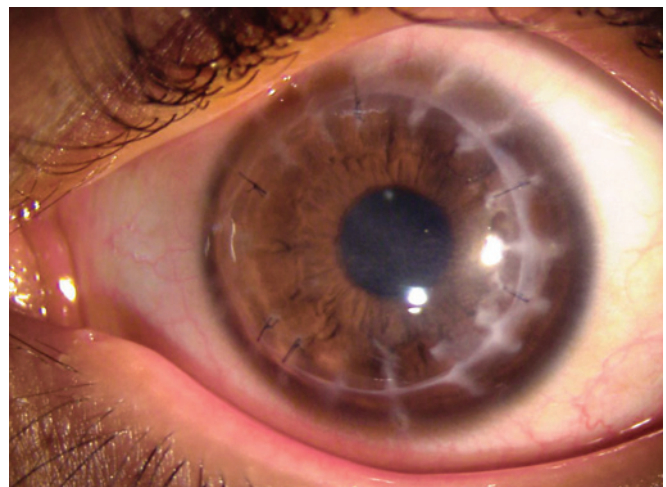
Figure 11 Deep anterior lamellar keratoplasty in a patient of keratoconus

Keratoconus

Keratoconus is a progressive, noninflammatory, corneal ectatic disorder characterized by protrusion of the cornea resulting in corneal distortion and decreased vision. There is progressive thinning along with steeping of the central cornea **(Fig. 10)**. Children in teenage years or early 20's are affected. The presenting features are diminution of vision for distance along with frequently changing spectacle refraction. It occurs bilaterally in most cases but disease develops asymmetrically.

Children have irregular astigmatism, photophobia and in late stages inability to see well with spectacles. Many cases of keratoconus have associated vernal keratoconjunctivitis. The disease generally worsens in the initial years with the process stopping by third to fourth decade. The clinical signs are:

- *Munson's sign:* Bulging of lower lid in downgaze.
- *Rizutti's sign:* Light focused temporally on cornea, is tightly focused inside nasal limbus.
- *Fleischer ring:* Partial or complete annular ring, yellowish brown to olive green in color containing hemosiderin pigment deposited at basal epithelium level.
- *Vogt's striae:* Vertical stress lines near apex of cone just anterior to Descemet's membrane.
  Prominent corneal nerves may occur as a network of grayish lines.

Management

Corneal topography helps in staging the disease and monitoring its progress.

Early cases documenting progression should undergo corneal collagen crosslinking (CXL). In this procedure, de-epithelized cornea is exposed to riboflavin dye (0.1% in dextran) and ultraviolet light, which strengthens the corneal stroma and arrests progression of ectasia. Other options include intracorneal ring segments (INTACS). Advanced cases with significant thinning are candidates for lamellar surgery. However, once Descemet's membrane is scarred, only option available is a full thickness penetrating keratoplasty **(Fig. 11)**. Keratoconus in pediatric age group may be seen at the age of 8–10 years and progresses very fast in this part of the Asian subcontinent. It is a common ocular manifestation in patients with Down syndrome. Topographical measures are very useful in diagnosing and following the progression in patients with keratoconus.

MORE ON THIS TOPIC

Garg P, Krishna PV, Stratis AK, Gopinathan U. The value of corneal transplantation in reducing blindness. Eye. 2005;19:1106-14.

Kankariya VP, Kymionis GD, Diakonis VF, Yoo SH. Management of pediatric keratoconus—evolving role of corneal collagen cross-linking: an update. Indian J Ophthalmol. 2013;61:435-40.

Stretton S, Gopinathan U, Willcox MD. Corneal ulceration in pediatric patients: a brief overview of progress in topical treatment. Paediatr Drugs. 2002;4:95-110.

Tseng SC. Acute management of Stevens-Johnson syndrome and toxic epidermal necrolysis to minimize ocular sequelae. Am J Ophthalmol. 2009;147:949-51.

Chapter 47.5
Uveitis
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Uveitis refers to the inflammation of the middle coat of the eyeball namely iris, ciliary body and choroid. Uveitis in children is not as common as in adults. However, the visual morbidity is high due to inability of the child to complain and consequent delayed presentation to the ophthalmologist. Children comprise 5–10% cases of any uveitis clinic. Although pediatric uveitis is rare, bilateral involvement and high visual morbidity leads to legal blindness in children. Even after control of inflammation the child may suffer from amblyopia. The presentation of uveitis is many times a part of a larger picture of systemic involvement. Hence, ophthalmologists and pediatricians have to work hand in hand to reach an appropriate diagnosis, ensure the best management and optimize the outcomes.

ETIOLOGY

Uveitis associated with juvenile idiopathic arthritis (JIA) and parsplanitis are reported to be common causes of noninfectious anterior and intermediate uveitis in children. Toxoplasmosis is the most common posterior infectious uveitis all over the world. In addition in developing country like India, tuberculosis and other parasitic diseases can also cause uveitis. Common causes of uveitis in children are given in **Box 1**.

PATHOGENESIS

Uveitis is a complex multifactorial disease of the eye, exact pathogenesis depends on specific etiology. However, it is proposed that both innate and adaptive immune responses may be the predominant mechanisms involved in the development of uveitis. Most uveitis diseases are considered polygenic with complex inheritance patterns and in virtually every polygenic disease studied there exists an human leukocyte antigen (HLA) genetic association as well.

CLINICAL FEATURES

Common symptoms include redness, pain and photophobia with or without defective vision. Sometimes squint or cataract may be the presenting feature especially in chronic uveitis associated with JIA. Some children with intermediate uveitis may complain of floaters. Common clinical signs seen in pediatric uveitis are given in **Table 1**.

Juvenile Idiopathic Arthritis

This entity is by far the most common association occurring with anterior uveitis in children. JIA is said to be associated with inflammation of joints of atleast 6 weeks duration in children less than 16 years.

It occurs in three forms:
1. *Systemic onset (Still's disease)* This occurs in approximately 20% of cases and consists of a flu like illness comprising of fever, maculopapular rash, lymphadenopathy and hepatosplenomegaly. Joint involvement is mild or absent initially. Uveitis rarely occurs in this subgroup.
2. *Polyarticular* This involves five or more joints and accounts for 40% of the cases of JIA. Girls are affected more commonly than boys. This type is further classified into rheumatoid arthritis (RA) factor positive and negative. Uveitis generally does not occur in patients who are RA factor positive.
3. *Pauciarticular* This involves four or lesser joints in the first 3 months of the onset of the disease. This form constitutes about 40% of the JIA cases but contributes to 70–90% of the JIA patients developing uveitis. This form is further subclassified into:

BOX 1 Common causes of uveitis in children

Anterior uveitis:
• Juvenile idiopathic arthritis
• Traumatic uveitis
• Trematode-induced uveitis
• Leptospiral uveitis
• Tuberculosis
• Herpes simplex virus
• Sarcoidosis
• HLA B-27 associated uveitis

Intermediate uveitis:
• Parsplanitis
• Tuberculosis
• Leptospirosis
• Sarcoidosis
• Multiple sclerosis

Posterior/pan uveitis:
• Endogenous endophthalmitis
• Toxocariasis
• Toxoplasmosis
• Tuberculosis
• Vogt-Koyanagi-Harada syndrome
• Sympathetic ophthalmia
• Intraocular foreign body
• Leukemia

Posterior uveitis with vasculitis:
• Cytomegalovirus
• Herpetic retinitis
• Behçet disease
• Sarcoidosis.

Table 1 Common clinical signs seen in uveitis in children

Systemic signs	Specific uveitis
Poliosis and hypopigmentation of skin	Vogt-Koyanagi-Harada syndrome, Sympathetic ophthalmia
Loss of hair	Systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome
Erythema nodosum	Inflammatory bowel disease, Tuberculosis, Sarcoidosis, Behçet disease
Oral and genital lesions	Behçet disease, Reiter disease, Syphilis
Oral ulcers	Systemic lupus erythematosus, inflammatory bowel disease
Epididymitis	Behçet disease, Tuberculosis
Arthralgias and arthritis	Seronegative spondyloarthropathies, JIA, Behçet disease, Sarcoid, SLE,
Lymph adenitis	Tuberculosis, Sarcoidosis, Lymphoma
Neuropathy	Herpes Zoster, Sarcoidosis
Hearing loss	Vogt-Koyanagi-Harada syndrome, Sarcoidosis
Respiratory symptoms	Tuberculosis, Sarcoidosis
Bowel disease	Whipple disease, Inflammatory bowel disease
Fever	Tuberculosis, Collagen vascular diseases, Leptospirosis

Abbreviations: SLE, systemic lupus erythematosus; JIA, juvenile idiopathic arthritis.

- *Type I:* This occurs predominantly in girls less than 5 years of age, most of whom are antinuclear antibodies (ANA) positive. This group has the highest risk for developing chronic iridocyclitis.
- *Type II:* Seen in older boys and also associated with recurrent acute anterior uveitis. Seventy-five percent of these boys tend to be HLA B-27 positive.

In general, arthritis antedates the occurrence of uveitis. Majority of the time, the presentation of intraocular inflammation is chronic, insidious, onset occurring in a white eye and is detected during a routine eye examination. Patient is always asymptomatic. Many a times parents complain of eye looking abnormal as a result of band-shaped keratopathy **(Fig. 1)** (whitish deposits on the cornea) or cataract or due to squinting of the eye. Hence, it is extremely important to screen these children regularly for atleast 7 years from the onset of arthritis or till the age of 12 years whichever is later. The ophthalmic screening schedule for patients with JIA is as follows:

- *Polyarticular*: Every 9 months
- *Polyarticular ANA positive*: Every 6 months
- *Pauciarticular*: Every 3 months
- *Pauciarticular ANA positive*: Every 2 months.

Juvenile Spondyloarthropathies

These are also referred to as seronegative spondyloarthropathies, which is a heterogeneous group of inflammatory joint diseases which are RA factor negative and strongly HLA B-27 positive. These disorders are more common in boys around the age of 10–12 years. Uveitis in this disorder is unilateral, nongranulomatous, acute, severe and always symptomatic.

Intermediate Uveitis

Intermediate uveitis is a chronic inflammation of the pars plana region (pars plana is the flat or smooth part of the ciliary body) which can be idiopathic or associated with a systemic disease. The idiopathic variety is referred to as pars planitis and is one of the common causes of uveitis in children.

Pars planitis is generally bilateral, presenting with symptoms of floaters, distorted vision due to macular edema or decreased vision due to macular scarring. The classic signs include snowball opacities and snow banking mainly on the inferior pars plana. Associated retinal findings include vasculitis, peripapillary retinal edema and cystoid macular edema.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology occurring in the age group of 8–15 years of age which can practically involve almost every organ. Uveitis is a common extrapulmonary manifestation. It may sometimes mimic JIA in its ocular and systemic presentation. Other ocular manifestations include:

- Lacrimal adenitis
- Conjunctival granulomas
- Episcleritis
- Scleritis
- Interstitial keratitis
- Optic neuritis
- Granulomatous anterior or panuveitis **(Fig. 2)**.

Diagnosis is clinched based on the biopsy, demonstrating noncaseating granulomas from the lacrimal gland, conjunctiva or from cutaneous nodules. In some cases spiral CT scan of the chest may be required to demonstrate the enlargement of the mediastinal lymph nodes. Serum angiotensin-converting enzyme levels are generally high in these patients and Mantoux test is negative. Familial juvenile systemic granulomatosis or Blau syndrome closely mimics sarcoidosis.

Behçet Disease

This is a multisystem disorder, ocular findings occur in 75–90% of the patients. Four major criteria for diagnosis include:

1. Recurrent oral ulcers
2. Genital ulcers
3. Skin lesions and
4. Recurrent uveitis.

The disease is referred to as complete if all four criteria are fulfilled and incomplete, if three criteria are fulfilled or one criterion and uveitis is present. Ocular signs comprise of typical mobile hypopyon, panuveitis, retinal vasculitis, occluded retinal vessels and retinal exudates. Diagnosis is generally clinical.

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada (VKH) syndrome results after an autoimmune reaction to the melanocyte containing tissues like uvea, ear, skin and meninges. It occurs more commonly among darkly pigmented races like as Orientals, Hispanics and African Indians. Although more common in the second to fourth decade, pediatric cases have been reported. Ocular findings comprise of bilateral panuveitis with multiple serous retinal detachments.

Figure 1 Bilateral band-shaped keratopathy in a patient with juvenile idiopathic arthritis

Figure 2 Granulomatous keratic precipitates and mature cataract in a child with sarcoid uveitis

The disease occurs in four stages:

1. *Prodromal stage (Stage I):* Headache, neck pain and tinnitus.
2. *Acute uveitis (Stage II):* Bilateral uveitis, exudative retinal detachment.
3. *Convalescent (Stage III):* Gradual depigmentation, alopecia, **(Fig. 3)** vitiligo, poliosis, retinal depigmentation.
4. *Chronic recurrent (Stage IV):* Relapsing uveitis with exacerbations.

Treatment is in the form of high dose intravenous/oral steroids and immunosuppressive drugs.

Ocular Toxoplasmosis

Ocular toxoplasmosis is the most common cause of posterior uveitis in children. It occurs due to infestation of the protozoan, *Toxoplasma gondii* which exists in various forms throughout its life cycle. The cat is the definitive host while humans are intermediate hosts. The clinical presentation varies depending on the time when the mother acquires infection during pregnancy, with transplacental transmission occurring in 40% of the cases. Retinitis and vitritis are hallmark signs in ocular involvement. Retinitis seen through the hazy vitreous is referred as *headlight in the fog* appearance. Recurrence of infection can occur and the reactivation occurs at the edge of a previously healed lesion. In some children scars over the macula can be responsible for loss of vision **(Fig. 4)**.

Figure 3 Alopecia in a child with Vogt-Koyanagi-Harada syndrome treated with heavy dose of oral steroids
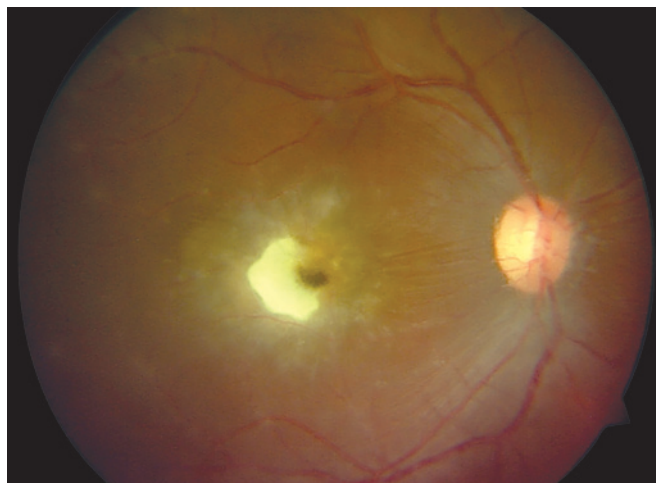
Diagnosis is mainly clinical, however raised antibody titers help in further substantiating the diagnosis. Clindamycin, azithromycin, sulfadiazine or pyrimethamine can be used to control the infection with oral steroids.

Ocular Toxocariasis

It is another common cause of posterior uveitis among the pediatric population. It is caused by dog roundworm, *Toxocara canis* found in 80% of the young dog and cat intestines. Infection usually occurs through ingestion of food or soil contaminated with dog/cat feces, containing the ova. Ova after reaching the intestine, produce larvae which then enter the blood and lymphatic circulation and reach liver, lungs and eye. Systemic infection is referred to as visceral larva migrans and may present as fever, cough, anorexia, malaise, seizures. Ocular toxocariasis is generally a unilateral disease which may present in three forms:

1. *Posterior pole granuloma:* The eye is externally quiet but the lesion leads to marked decrease in vision or white reflex in the pupillary area.
2. *Peripheral granuloma:* A yellowish white elevated lesion is seen in the peripheral part of retina. An associated traction band resulting in macular displacement, decreased vision and squint may also be seen.
3. *Endophthalmitis:* Occurs due to posterior segment inflammation.

Diagnosis is mainly clinical, supported by leukocytosis and eosinophilia and positive antibody titers on enzyme-linked immunosorbent assay. Topical and systemic steroids are given to control the inflammation.

Trematode-Induced Uveitis

Trematode-induced uveitis is a newly recognized pediatric uveitis reported in children less than 16 years of age in South India. A significant history associated with this uveitis is bathing or swimming in river or pond water, where the snails are infested with trematode larvae. Granulomas bigger than 3 mm are usually surgically excised; smaller lesions respond to a course of topical steroids **(Fig. 5)**.

Viral Uveitis

Herpetic anterior uveitis is usually unilateral, associated with acute granulomatous pigmented keratic precipitates, iris atrophy, pupillary irregularities and rise in intraocular pressure. Posterior segment viral infection results in acute retinal necrosis

Figure 4 Fundus picture showing healed as well as reactivation of toxoplasmosis retinochoroiditis
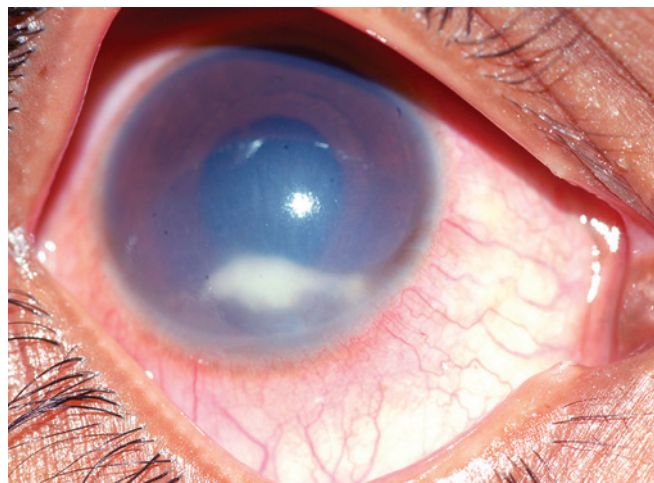
Figure 5 Trematode granuloma in the anterior chamber of the eye in a child

characterized by peripheral retinitis patches, dense vitritis and retinal arteritis with or without high intraocular pressure.

Cytomegalovirus is a common opportunistic infection occurring in immunocompromised children with AIDS, especially those with low CD4 counts. Ocular findings are multifocal brushfire retinitis with hemorrhagic borders along retinal vessels. This kind of uveitis requires aggressive systemic antivirals in the form of oral valacyclovir, ganciclovir and foscarnet in addition to treatment for immunosuppression.

Tuberculous Uveitis

Tuberculosis is an endemic infective disease; primary focus of infection is mainly in the lungs, however practically any organ of the body can be affected. Ocular findings comprise of:

- Chronic bilateral granulomatous uveitis with mutton fat keratic precipitates
- Unifocal or multifocal choroidal tubercles **(Fig. 6)**
- Retinal vasculitis
- Vitritis, and
- Optic disc granuloma.

Definitive diagnosis is made by identifying the bacilli in the aqueous or vitreous either by smear and culture or by molecular diagnostics. A positive tuberculin skin test (Mantoux test) and radiological studies may aid in clinical diagnosis. Antituberculous drugs are given for around 6 months along with oral steroid after initial few weeks of anti-tuberculosis treatment to control the inflammation. Hypersensitivity reaction to tubercular protein may result in phlycten in children **(Fig. 7)**.

Cysticercosis

Cysticercosis is a parasitic infection caused by *Cysticercus cellulosae* which is the larval form of tapeworm *Taenia solium*. Humans are definitive hosts and pigs are intermediate hosts. Transmission occurs through ingestion of undercooked meat, uncooked vegetables or contaminated water. Ocular findings consist of subconjunctival cyst, anterior chamber cyst or subretinal cysts. Cysts can be surgically removed **(Figs 8A and B)**. Medical management includes Albendazole (400 mg/day, oral for 14 days) and oral steroids (1 mg/kg body weight in tapering dose for 2–3 weeks) especially in patients with ruptured cyst.

Endogenous Endophthalmitis

Endogenous endophthalmitis occurs as a result of hematogenous spread of bacteria. The source may be a nonocular infective focus.

Fungal endogenous endophthalmitis is common after intravenous fluids because of contaminated medical supplies. Vitrectomy, intravitreal antibiotics along with systemic antibiotics can control the infection.
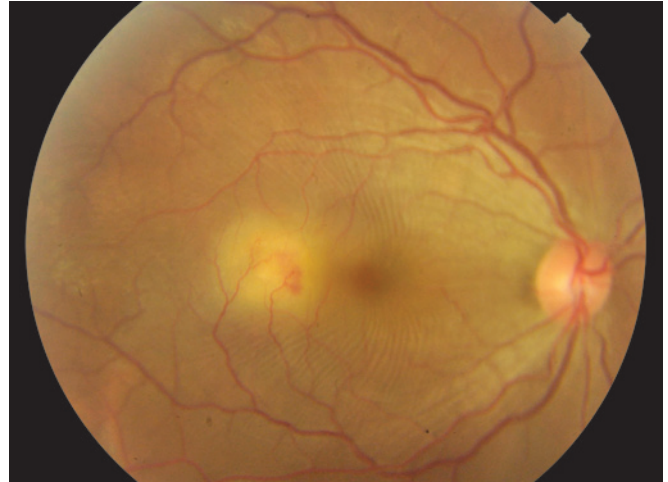
Figure 6 Fundus picture showing tubercular choroidal granuloma near macula

Figure 7 Phlyctenular conjunctivitis in a child with tuberculosis
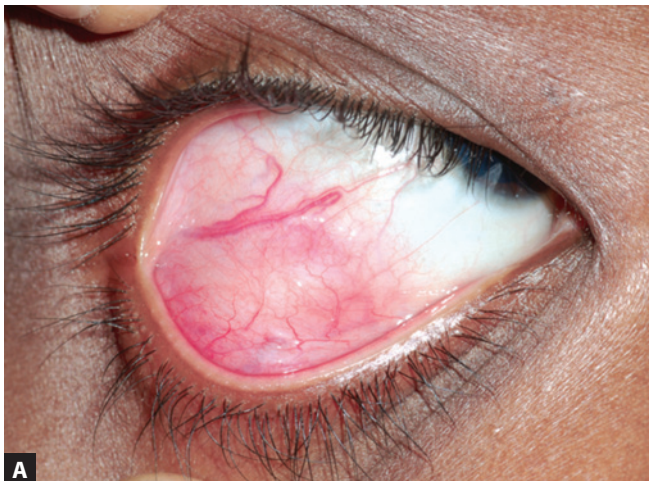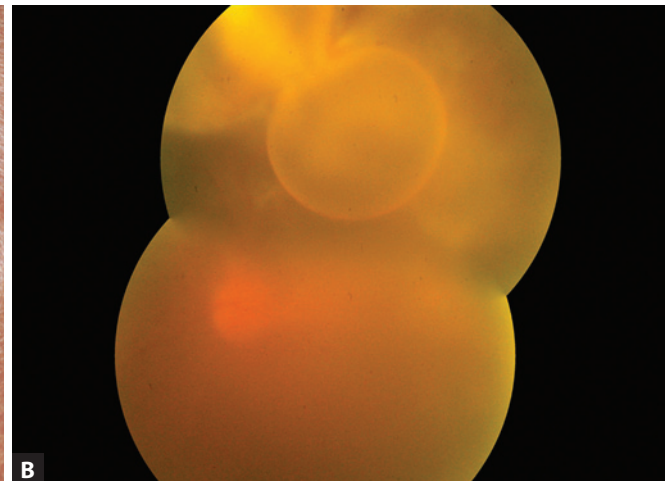
Figures 8A and B (A) Subconjunctival cysticercosis; (B) Fundus picture showing an intact cysticercosis

Masquerade Syndromes

Masquerade syndromes are conditions where the presence of noninflammatory cells in the eye mimic the inflammatory cells of uveitis. Some examples include juvenile xanthogranuloma, leukemic infiltrates and retinoblastoma.

MANAGEMENT

Investigations for uveitis are aimed to establish the etiology **(Box 2)**. The basic principles for treatment in uveitis are as follows:

- To treat infectious causes of uveitis specifically, e.g., tuberculosis, viral and toxoplasmosis
- To treat noninfectious uveitis with steroids in an appropriate form and regimen to control the inflammation
- To use immunomodulatory agents if patient has steroid-induced complications or uveitis unresponsive to steroids. Drugs such as methotrexate, azathioprine and mycophenolate mofetil are used in children
- To keep the pupil mobile with dilating eye drops to avoid structural damage.

Anterior Uveitis

Corticosteroid eye drops are administered in tapering dosage. It is normally started six times a day in cases of mild to moderate inflammation and half to one hourly in cases of severe inflammation **(Tables 2 and 3)**. A mydriatic cycloplegic like homatropine or cyclopentolate is added to relieve ciliary spasm and to prevent posterior synechiae. Now a days atropine is rarely used in children for uveitis. It is better to keep the pupil mobile, by using homatropine rather than keeping it fully dilated with atropine. Formation of 360° posterior synechiae in fully dilated pupil makes the patient more symptomatic.

Intermediate Uveitis

Periocular steroid injection via posterior subtenon is given in cases of unilateral presentation **(Fig. 9)**. Oral steroids are preferred in

Table 2 Topical medications commonly used in uveitis

Steroid eye drops	*Mydriatics-cycloplegic eye drops*
Dexamethasone 0.1%	Atropine 1%
Prednisone acetate 1%	Homatropine 2%
Prednisone sodium phosphate 1%	Cyclopentolate 1%
Fluorometholone 0.1%	Tropicamide 1%
Loteprednol 0.2, 0.5%	Phenylephrine 10%
Difluprednate 0.05%	

Table 3 Route of administration, dose and common adverse reactions of steroids used in uveitis in children

Route of administration steroids	*Dose*	*Common side effects*
Topical	*Hourly:* Severe inflammation *6–8 times:* Moderate inflammation	Glaucoma, cataract
Periocular/subtenon	Triamcinolone acetate 40 mg in 1 mL	Cataract, glaucoma, scleral thinning
Intravitreal	Triamcinolone acetate 4 mg in 0.1 mL	Cataract, glaucoma, endophthalmitis
Intravitreal steroid implant	Dexamethasone 0.7 mg	Cataract, glaucoma, endophthalmitis
Oral prednisolone	1 mg/kg/day	Peptic ulcer, weight gain, increase in blood sugar, osteoporosis, growth retardation, aseptic necrosis of femoral head
Intravenous methylprednisolone	500 mg once a day for 3 days	Headache, increase in blood sugar

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> **BOX 2   Laboratory investigations for uveitis in children**
>
> *Anterior uveitis*:
> - *Complete blood count:* Infections, leukemia
> - *Antinuclear antibodies:* JIA
> - *ESR:* JIA, TB
> - *Serum angiotensin-converting enzyme (ACE):* Sarcoidosis
> - *Serum lysozyme:* Sarcoidosis
> - *Serum calcium:* Sarcoidosis
> - *HLA B27:* Seronegative spondyloarthropathies
> - *X-ray/ MRI spine:* Ankylosing spondylitis
> - *X-ray chest:* TB, sarcoidosis
> - FTA-ABS: Syphilis
>
> *Intermediate uveitis*:
> - *X-ray chest:* TB, sarcoidosis
> - *Tuberculin skin test (Mantoux test):* TB
> - Serum ACE levels
> - PCR, ELISA for Toxocariasis
> - FTA-ABS for syphilis
>
> *Posterior uveitis*:
> - ELISA-toxoplasma titers
> - ELISA-toxocara titers
> - TORCH titers (Antibody titers for *Toxoplasma*, rubella, CMV and herpes) especially in newborns
> - ELISA for Lyme disease
> - Serum lysozyme
> - Serum ACE levels
>
> *Abbreviations*: ELISA, enzyme-linked immunosorbent assay; CMV, Cytomegalovirus; JIA, juvenile idiopathic arthritis; ESR, erythrocyte sedimentation rate; FTA, fluorescent treponemal antibody; PCR, polymerase chain reaction.

Figure 9 Posterior subtenon depot steroid injection given in upper outer quadrant of left eye. Patient is looking down and right

bilateral disease. In recurrent cases, systemic immunomodulatory treatment may be needed. Pars plana vitrectomy can be performed to clear the opaque vitreous.

Posterior and Panuveitis

Steroids form the backbone of treatment of intraocular inflammation. They are administered in oral, intravenous, periocular

Figure 10 Cushingoid facies in a child

and intravitreal route depending on the location and severity of inflammation. In general, once the uveitis is under control for 3 months with treatment, steroids can be stopped. Then the patients are reviewed once in 3 months. Children with JIA are followed until 18 years. Children on oral and topical steroids are regularly screened for complicated cataract and glaucoma. They often develop cushingoid features after prolonged oral steroids **(Fig. 10)**.

Immunomodulatory therapy, mainly methotrexate is added when the response is poor with steroids or when they develop iatrogenic complications like cataract or glaucoma **(Table 4)**.

MORE ON THIS TOPIC

Cunningham ET. Uveitis in children. Ocul Immunol Inflamm. 2000;8:251-61.

De Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol. 2003;87:879-84.

Kalinina Ayuso V, ten Cate HAT, van den Does P, et al. Young age as a risk factor for complicated course and visual outcome in intermediate uveitis in children. Br J Ophthalmol. 2011;95:646-51.

Table 4 Immunosuppressants used in uveitis in children

Drug	Mechanism of action	Dosage	Complications
Antimetabolites			
Methotrexate	Folate analogue, inhibits dihydrofolate reductase	7.5–20 mg/week	GI upset, fatigue, hepatotoxicity, pneumonitis
Azathioprine	Alters purine metabolism	50–150 mg/day	GI upset, hepatotoxicity
Mycophenolate mofetil	Inhibits purine synthesis	1–3 g/day	Diarrhea, nausea
T-cell inhibitors			
Cyclosporine	Inhibits T-cell activation	2.5–5 mg/kg/day	Nephrotoxicity, Hypertension, Gingival hyperplasia, gastrointestinal upset, paresthesias
Tacrolimus	Inhibits T-cell activation	0.2 mg/kg/day	Nephrotoxicity, hypertension, diabetes mellitus

Rao NA. Uveitis in Children. In: Wright K, Spiegel P. Textbook of Pediatric Ophthalmology and Strabismus. 2nd ed. Springer; 2013. pp. 499-522.

Rathinam SR, Babu M. Algorithmic approach in the diagnosis of uveitis. Indian J Ophthalmol. 2013;61:255-62.

Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol. 2007;55:173-83.

Sheppard JD, Davis J, Meier A. The Challenges of Pediatric Uveitis. In: Wilson ME, Saunders RA, Trivedi RH. Pediatric Ophthalmology: A Current Thought and A Practical Guide. Springer; 2009. pp. 419-48.

Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. Ophthalmology. 2009;116:1544-51.

Tugal-Tutkun. Pediatric Uveitis. J Ophthalmic Vis Res. 2011;6:259-69.

Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. Ocul Immunol Inflamm. 2013;21:478-85.

Chapter 47.6
Cataract and Lens-Related Issues

Abhay R Vasavada, Sajani K Shah

Pediatric cataract is the most common cause of treatable childhood blindness, accounting for 5–20% of blindness in children worldwide. The prevalence of childhood cataracts has been reported to be in the range of 1–15 per 10,000 children. The incidence has been reported as 2.5/10,000 by the age of 1 year, increasing to 3.5/10,000 by age 15. It is estimated that over 200,000 children are blind from disorders of the lenses.

EMBRYOLOGY AND GROWTH

Primary lens fibers expel their intracellular content, and form an optically clear embryonic nucleus measuring 0.35 mm in diameter during the sixth week of gestation. Equatorial, secondary lens fibers migrate anteriorly and posteriorly to meet each other at the anterior upright Y and posterior inverted Y sutures. These sutures demarcate the embryonic and fetal nucleus. The secondary lens fibers continue to form the fetal nucleus up to the 8 months of gestation. Both fetal and embryonic nuclei are present at birth. After birth, the equatorial fibers grow and elongate to form the cortex. The developing lens requires nutrition that is obtained through the tunica vasculosa lentis. This gradually starts regressing after the eighty-fifth day, and completely regresses by the seventh month. At term, only wispy remnants of the pupillary membrane are left, and a vestigial hyaloid artery (Mittendorf's dot) may often be attached to the axial posterior surface of the lens.

Abnormalities of the pediatric lens may either be isolated cases or may be associated with diseases of the urinary tract, central nervous system, or skeletal system. Disorders of the pediatric lens include, in addition to cataract, abnormalities of shape (spherophakia, coloboma), size (microspherophakia, disciform eye), location (subluxation or dislocation of lens), and development [persistent fetal vasculature (PFV)].

CLASSIFICATION

Classification of lenticular opacities based on their anatomical location **(Table 1)** facilitates precise localization of the lens opacities. Using the location of the opacities, meaningful information can be derived about the visual prognosis, timing, and nature of the insult and its progression. It can also aid in the identification of associated ocular and systemic anomalies. Moreover, it also helps the surgeon in planning appropriate management strategies.

Anterior Cataract

Anterior Polar Cataract
Anterior polar cataracts are often hereditary, and visually insignificant. However, notable exceptions do occur. The most common type of anterior polar cataract presents as a tiny white dot in the center of the anterior capsule. These cataracts are usually bilateral, but may be unilateral and probably represent a mild abnormality of lens vesicle detachment. They are usually 1 mm or less in diameter and generally do not progress in size. Corneal astigmatism may be present, however, and can cause amblyopia. These pyramidal cataracts are almost always bilaterally symmetric and may be dominantly inherited. Anterior lenticonus is less common than the posterior variety and is usually associated with Alport syndrome.

Table 1 Congenital lens abnormalities

Anatomical type	Subtypes
Anterior capsular cataract	• Anterior polar • Anterior capsular • Anterior capsular plaque
Cortical cataract	• Anterior cortical • Posterior cortical • Membranous
Nuclear cataract	• Isolated nuclear • Lamellar • Sutural • Punctate
Posterior capsular cataract	• Posterior polar • Posterior subcapsular • Posterior lenticonus
Total cataract	
Mixed cataract	
Cataract with pre-existing posterior capsule defect	
Cataract with persistent fetal vasculature	

Anterior Capsular Cataract
Anterior subcapsular cataracts are often associated with trauma, radiation, or acquired diseases such as uveitis, Alport syndrome (cataracts associated with anterior lenticonus), and atopic skin diseases (shield-like anterior subcapsular cataracts are classic). Anterior subcapsular opacities may also be part of a more widespread multilayer cataract.

Anterior Capsular Plaque
These are axial opacities in the capsular epithelium **(Fig. 1)**. They are often associated with total white cataract, but due to lack of contrast, the diagnosis is often missed preoperatively. They occur either as multiple plaques distributed throughout the anterior lens epithelium or as a single large plaque, which may be located centrally or eccentrically. They are commonly associated with a persistent pupillary membrane and/or microcornea.

Cortical Cataract

Anterior and Posterior Cortical Cataract
Isolated cortical cataract is less common in infants and young children, **(Figs 2 and 3)** and posterior cortical cataract is more common than anterior cortical cataract. Cortical cataract is usually
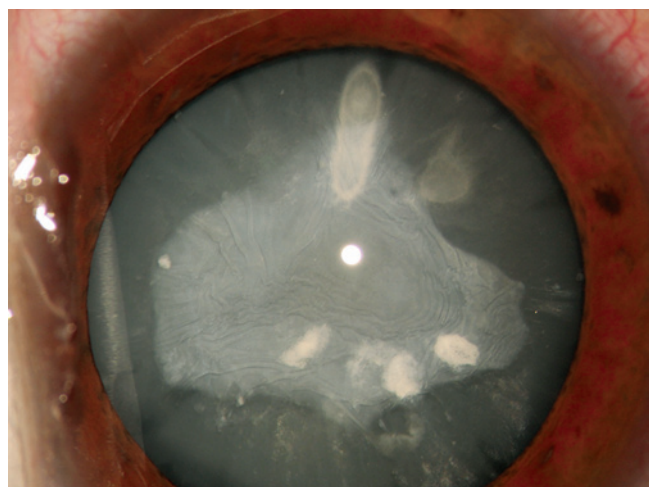
Figure 1 Anterior capsule plaque
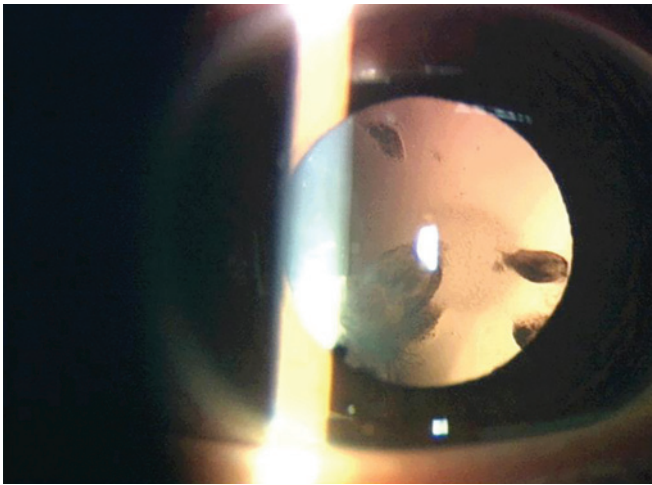
Figure 2 Anterior cortical cataract

Figure 3 Posterior cortical cataract

present as club-shaped opacities in the peripheral zone of the lens cortex, which does not interfere with vision. On rare occasions, the presence of diabetes mellitus can cause cortical opacities in teenage children. The classically described *coronary cataract* is a type of deep cortical cataract. It is bilateral and stationery. Usually sporadic, this is a developmental cataract that is diagnosed around puberty and is not visually significant in most cases. The blue dot cataract is a type of cortical cataract.

Membranous Cataract

Membranous cataract is an advanced form of cortical cataract, in which the entire lens substance is absorbed, leaving a thin gray-white capsular membrane that replaces the cortex **(Fig. 4)**. It is frequently bilateral and visual prognosis is poor. It is often associated with aniridia and in congenital rubella, it occurs as a sequence of intrauterine iridocyclitis that remains active after birth, leading to PFV or microphthalmos. It has been described in Lowe's syndrome. Most cases are sporadic and a familial or dominant transmission is rare.

Nuclear Cataract

Isolated Nuclear Cataract

This has been classically described as a *central pulverulent cataract*. The opacity involves the embryonic nucleus. It is caused

by an insult occurring during the first 3 months of development. It is always bilateral and nonprogressive. The white, discrete dots appear as a granular disc in the center of the lens and sometimes the dot-like opacities may extend into the overlying cortex. Known as the *blue dot cataract*, it is visually insignificant and is diagnosed only on routine slit-lamp examination.

Rubella Cataract

This cataract accounts for 4–5% of all congenital cataracts in developing countries **(Figs 5 and 6)**. The infection is contracted by the mother during the first 3 months of pregnancy. Rubella is bilateral, progressive, and may be associated with microphthalmos. It may present as dense nuclear cataract or as total cataract soon after birth. Membranous cataract is also commonly found in these eyes. This cataract has demonstrated a strong autosomal dominant inheritance. Salt and pepper retinopathy may coexist.

Lamellar Cataract

Lamellar cataracts **(Fig. 7)** are usually acquired rather than congenital. They involve a layer (lamellae) of cortex surrounding the fetal nucleus, peripheral to the Y sutures. They are almost always bilateral, but are commonly asymmetric. The visual prognosis is usually better with lamellar cataracts (even when surgery is delayed) than with cataract types that are densely opaque at birth such as fetal nuclear opacities (discussed here). This improved
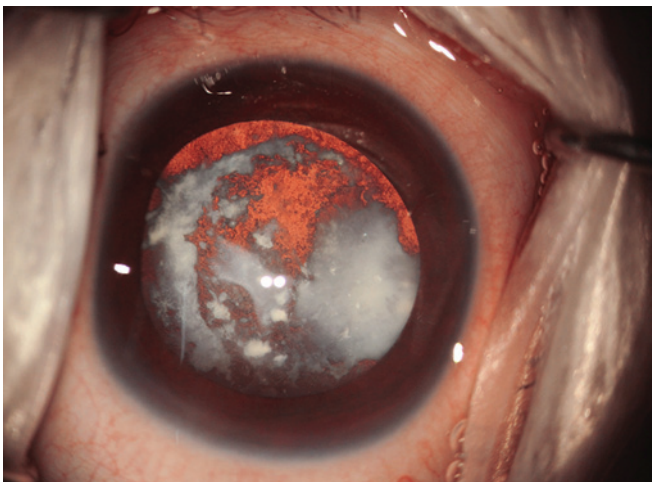
Figure 4 Membranous cataract

Figure 5 Rubella cataract. Typical floriform appearance of the cataract
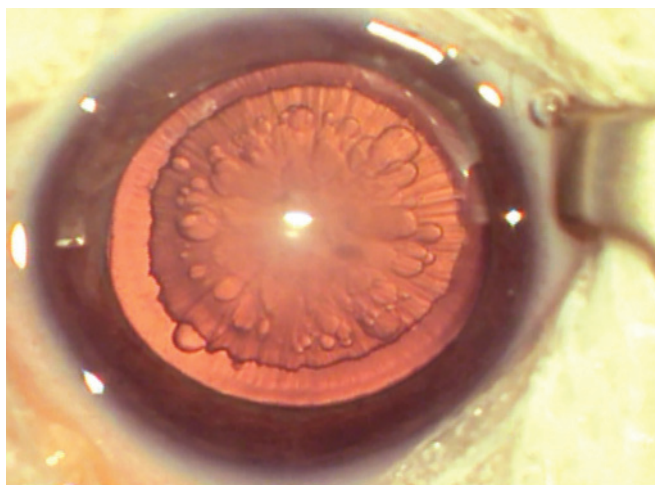
Figure 6 Rubella cataract

Figure 7 Lamellar cataract, slit view

prognosis is attributed to the late development of cataract. Due to this late onset, during the critical period of visual development, the cataract does not preclude normal visual development. Initially lamellar cataracts are characteristically mild and they slowly worsen with time. Remarkably, children can sometimes function quite well visually even when the lamellar opacity blackens the retinoscopic refraction completely. These cataracts are usually about 5–6 mm in diameter and characteristically have a thin layer of clear cortex external to the opacity. The nucleus, internal to the cataract, is also characteristically clear.

Lamellar cataracts are often hereditary, following an autosomal dominant transmission pattern. In sporadic cases of the congenital form, cataract can be attributed to a parathyroid deficiency resulting in hypocalcemia and avitaminosis-D in the mother during the last trimester of pregnancy or in the fetus. In such cases, cataract is frequently associated with imperfect calcification of the enamel of the teeth.

The developmental form could be associated with infantile tetany (carpopedal spasm, general convulsions and laryngismus stridulus) and rickets. Untreated galactosemia classically causes an oil droplet **(Fig. 8)** or a lamellar cataract in infancy. A developmental (postnatal) lamellar cataract can arise in premature infants.

Sutural Cataract
It is a Y-shaped opacity affecting one or both the sutures of the fetal nucleus **(Fig. 9)**. The opacity is either around the suture or involves

the sutures, more posterior than anterior. Opacification of both anterior and posterior sutures is called *stellate cataract.* They are stationary, bilateral and visually insignificant. Occasionally, they may progress to form nuclear or central cataracts. This could be present in obligate carriers of the Nance-Horan syndrome (supernumerary teeth, prominent teeth and ears, and developmental delay).

Punctate Cataract
The floriform and coralliform cataracts are types of nuclear cataract which follow an autosomal dominant inheritance pattern. In floriform cataract, clusters of opacities are present around the fetal sutures. Sometimes they extend into the cortex, which indicates their development after birth. They are transmitted as a dominant trait and could be associated with camptodactyly. Coralliform cataract has large crystals accumulated in the center of the lens without reference to the sutures.

Posterior Capsular Cataract

Posterior Polar Cataract
Posterior polar cataracts are usually sporadic cortical opacities with a propensity for spontaneous posterior capsule rupture. These cataracts can be unilateral or bilateral, mild or severe. Surgeons should exercise caution while performing surgery for posterior polar opacities since the posterior capsule may already be ruptured or honeycombed into a weakened meshwork.

Figure 8 Oil droplet cataract in galactosemia
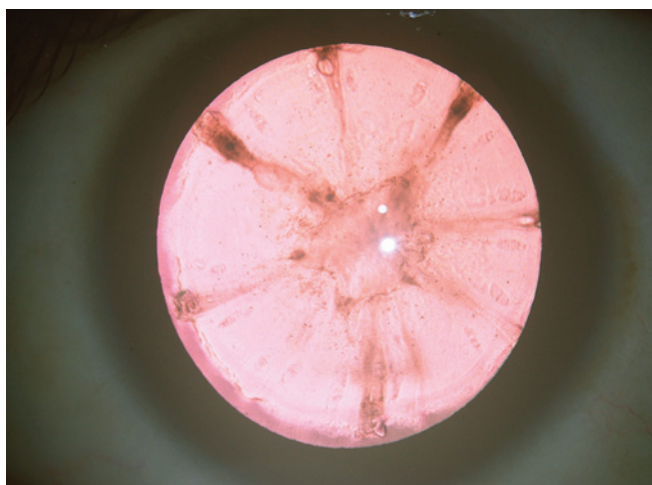
Figure 9 Sutural cataract with punctate cortical opacities

Posterior Subcapsular Cataract

This form of cataract is seen as vacuolar or plaque-like opacities close to the posterior capsule. Typically it is seen in older children following trauma, uveitis secondary to rheumatoid arthritis, or after prolonged use of steroids for spring catarrh and radiation. Plaque-like opacities, myotonic dystrophies and Turner's syndrome may be seen in congenital cataract.

Posterior Lenticonus

Posterior lentiglobus **(Fig. 10)** is mostly unilateral and is not associated with microphthalmia. It represents the most common type of developmental cataract in a normal-sized eye. Most forms are sporadic, but occasionally an autosomal-dominant inherited bilateral form may be encountered. The lens changes begin in the posterior capsule, possibly secondary to a weakness in the area of prior contact with the hyaloid artery. The bulge in the posterior capsule is usually not present at birth, but becomes more exaggerated as intralenticular pressure increases with age.

Total Cataract

It presents as a general opacity of all the lens fibers **(Fig. 11)**. This occurs due to an insult acting throughout the period of development or a severe insult late in fetal life. Some lenses are completely opaque when first diagnosed; in other cases they develop from lamellar or nuclear cataracts. They are frequently bilateral. In cases of early onset, they have a profound effect on visual development and may often mask underlying posterior capsule defects or posterior segment pathologies. Total cataract is frequently reported with congenital rubella syndrome, Down's syndrome, acute metabolic or even sporadic cataracts. Aggressive surgical management is mandatory for good visual prognosis.

Mixed Cataract

Instead of isolated opacities, often, several anatomic types of cataract coexist in the same eye. Depending on the type and severity of opacities, vision may be affected.

Pre-existing Posterior Capsule Defect

It has been reported that pre-existing posterior capsule defect occurs in about 6.75% of Indian eyes. They present bilaterally and are progressive. Unilateral posterior capsule defects begin as a posterior lentiglobus. It is recognized by the presence of well-demarcated, thick defect margins and white dots on the posterior capsule and in the vitreous **(Figs 12A to C)**. When the globe is moved with forceps, the dots in the anterior vitreous move like a fish tail (fish-tail sign). These are frequently camouflaged by a mature cataract.

ETIOLOGY

Numerous individual causes of cataract exist, and often, multiple factors act together, with plenty of scope for overlap between
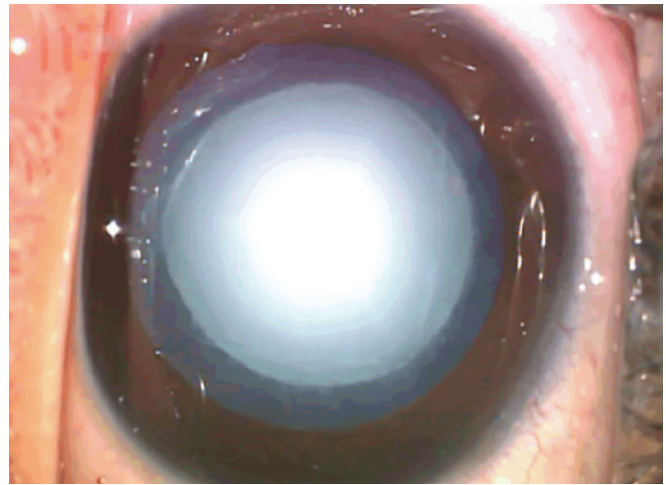
Figure 11 Total white cataract
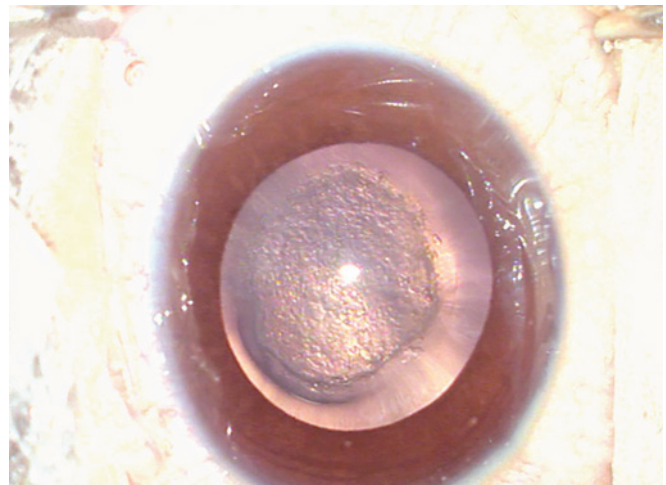
Figure 10 Posterior lenticonus (lentiglobus). The posterior lens capsule is seen bulging posteriorly

the groups. Some causes predispose to a specific morphological variety of cataract. Moreover, a given cause may produce more than one morphological form of cataract. Etiological classification of congenital cataract is provided in **Box 1**.

Ectopia Lentis

Subluxation or dislocation of the crystalline lens is a condition in which the crystalline lens is either partially or completely dislocated from its original position, due to absence or weakness of the zonules. In children, this has been associated with several clinical conditions **(Table 2)**.
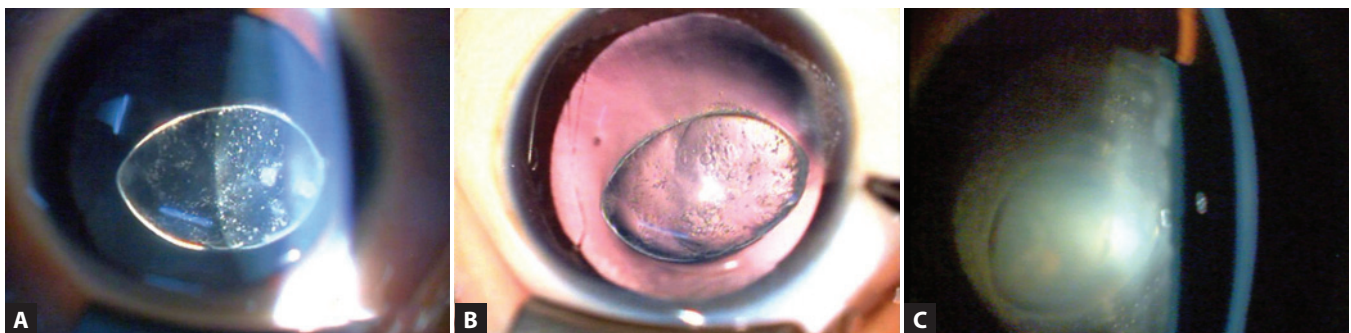
Figure 12A to C Classical pre-existing posterior capsule defect. (A to C) Well-demarcated margins of a pre-existing posterior capsule defect

BOX 1 Etiological classification of congenital cataracts

Isolated findings

Hereditary
• Autosomal dominant:
  – Autosomal recessive
  – X linked
Sporadic (one-third of all congenital cataracts)

Part of syndrome or systemic disease:

Hereditary

• *With renal disease:*
  – Oculocerebrorenal syndrome (Lowe syndrome)
  – Alport syndrome (autosomal dominant)
• *With central nervous system disease:*
  – Marinesco sjögren syndrome (autonomic recessive)
  – Sjögren's Syndrome (autonomic recessive)
  – Smith-Lemli-Opitz syndrome
  – Laurence-Moon-Bardet-Biedl syndrome
• *With skeletal disease:*
  – Conradi syndrome (presence of cataract indicates worse prognosis)
  – Marfan syndrome
  – Stippled epiphyses
• *With abnormalities of the head and face:*
  – Hallermann-Streiff syndrome
  – François dyscephalic syndrome
  – Pierre Robin syndrome
  – Oxycephaly
  – Crouzon disease
  – Acrocephalosyndactyly (Apert syndrome)
• *With polydactyly:*
  – Rubinstein-Taybi syndrome
• *With skin disease:*
  – Bloch-Sulzberger syndrome
  – Congenital ectodermal dysplasia of the anhidrotic type
  – Rothmund-Thomson syndrome, Siemens syndrome
  – Incontinentia pigmenti
  – Atopic dermatitis
  – Cockayne syndrome
  – Marshall syndrome

• *With chromosomal disorders:*
  – Trisomy 13 (usually die within 1 year)
  – *Trisomy 18*: Edward syndrome
  – *Trisomy 21*: Down syndrome (often cataract formation delayed until an approximate age of 10 years)
  – Turner syndrome
  – Patau syndrome
• *With metabolic disease:*
  – Galactosemia (autosomal recessive)
  – Galactokinase deficiency
  – Congenital hemolytic jaundice
  – Fabry disease
  – Refsum disease
  – Mannosidosis
• *With miscellaneous hereditary syndromes:*
  – Norrie disease
  – Hereditary spherocytosis
  – Myotonic dystrophy

Nonhereditary

• *Prenatal causes:*
  – Rubella syndrome
  – Toxoplasmosis
  – Varicella
  – Cytomegalovirus
  – Herpes simplex virus
  – Measles
  – Vaccinia
  – Intrauterine hypoxia or malnutrition

• *Postnatal causes:*
  – Retinopathy of prematurely
  – Hypoglycemia
  – Hypocalcemia
  – Radiation
  – Trauma
  – Chronic uveitis
  – Diabetes mellitus
  – Wilson's disease
  – Renal insufficiency
  – Drug-induced
  – High voltage electric shock.

• *Associated with another ocular abnormality:*
  – PFV (persistent fetal vasculature)
  – Microphthalmos
  – Aniridia
  – Retinitis pigmentosa
  – Norrie disease
  – Colobomas
  – Lenticonus

Table 2 Conditions associated with subluxated/dislocated lenses

Systemic conditions
• Marfan syndrome • Homocystinuria • Weill-Marchesani syndrome • Ehler-Danlos syndrome • Hyperlysinemia • Sulfiteoxidase deficiency
Ocular conditions
• Aniridia • Iris coloboma • Trauma • Hereditary ectopia lentis

Marfan Syndrome

It is an autosomal dominantly inherited systemic disease, with variable penetrance. It is the disease most commonly associated with dislocated lenses. The syndrome consists of abnormalities of the cardiovascular, musculoskeletal, and ocular systems. It is caused by mutations in the fibrillin gene on chromosome 15. Physical characteristics of affected individuals include tall stature, arachnodactyly, loose, flexible joints, scoliosis and chest deformities. Cardiovascular abnormalities are a source of significant mortality and may be in the form of a dilated aortic root, ascending aorta, dissecting aortic aneurysm, and a floppy mitral valve. Ocular abnormalities occur in 80% of patients, including ectopia lentis, myopia, and greater risk of retinal detachment. Typically, the lens is dislocated upward and temporally.

Homocystinuria

It is a rare, autosomal recessive condition. It is caused by an abnormality in the enzyme cystathionine β-synthase, causing accumulation of homocysteine in the plasma, which is then excreted through the urine. Clinical features are variable, affecting the eye, skeletal system, central nervous system, and vascular system. Ocular findings primarily consist of dislocated lenses (frequently downward and nasally). Systemically, vascular complications are common and secondary to thrombotic disease affecting large or medium-sized arteries and veins all over the body. Patients are usually tall, with osteoporosis, scoliosis, and chest deformities.

Ectopia Lentis Et Pupillae

Ectopia lentis et pupillae is a rare autosomal recessive condition. It is manifested by bilateral displacement of the pupil, usually inferotemporally, with lens dislocation in the opposite direction.

Persistent Fetal Vasculature

Persistent fetal vasculature, previously known as persistent hyperplastic primary vitreous, is a developmental ocular anomaly in which the embryonic hyaloid vasculature fails to regress normally. The disease entity of PFV has a wide spectrum with varying degrees of persistent components of the fetal hyaloid system. This may be as mild as pupillary strands or a small central/paracentral posterior capsular opacification (Mittendorf's dot) or as severe as a retrolenticular membrane, retinal dysplasia, and retinal detachment. PFV may be anterior, posterior, or both depending on which ocular structures are involved.

MANAGEMENT OF CATARACT

Surgery is the primary mode of therapy. Visually significant cataract in children calls for prompt surgical intervention to clear the ocular media and provide a focused retinal image. The timing of treatment is crucial for visual development and successful rehabilitation of children, especially during early infancy. In case of a unilateral dense cataract diagnosed at birth, the surgeon can wait until the patient is 4–6 weeks of age. This decreases anesthesia-related complications and facilitates the surgical procedure. Waiting beyond this time, however, adversely affects the visual outcome. In the case of bilateral cataract diagnosed at birth, a good visual outcome can be achieved if the child is operated before 10 weeks of age. It is important to keep the time interval between surgeries performed on the two eyes to a minimum.

Simultaneous cataract surgery on both eyes is performed only when anesthesia poses a higher than average risk, or if the patient lives far away and a second visit for a surgery on the second eye may be difficult.

Pediatric cataract needs a special surgical strategy as these eyes have greater elasticity of the capsule, lower scleral rigidity, higher incidence of inflammation and posterior capsule opacification (PCO), a thick vitreous gel, and a small growing eye. A discussion on techniques of surgery is beyond the scope of this chapter.

Intraocular Lens Implantation

Options for optical correction following pediatric cataract surgery are primary IOL implantation, aphakic glasses and contact lenses. Primary IOL implantation has become a preferred approach in children above 2 years. Implanting an IOL is still controversial in children under 2 years, especially those under 1 year, as the safety of IOL implantation in these eyes is not proven. Eyes with juvenile rheumatoid arthritis, microcornea, microphthalmos and severe PFV may be considered as contraindications for IOL implantation.

Intraocular lens implantation in children has the benefit of providing at least partial optical correction which aids in visual development especially in eyes prone to amblyopia. Advances in surgical techniques and instrumentation, combined with implantation of better quality IOLs has now resulted in fewer IOL-related complications in children. This encourages more and more surgeons to use IOLs even in very young children. For bilateral cataract during this first year, aphakic glasses and/or contact lens use may be a reasonable option. However, for unilateral cataract, it is still controversial whether to offer primary IOL implantation at the time of infantile cataract surgery.

Both polymethylmethacrylate and hydrophobic acrylic foldable IOLs have been widely used in pediatric eyes. However, several studies have now shown that hydrophobic acrylic IOLs are preferable as they offer better uveal biocompatibility and decreased incidence of visual axis opacification (VAO), with hydrophobic acrylic IOLs causing a delayed onset of PCO. In-the-bag fixation is the most preferred site of IOL implantation, although IOL may also be implanted in the ciliary sulcus in cases of inadequate posterior capsular support.

COMPLICATIONS OF PEDIATRIC CATARACT SURGERY

Visual Axis Opacification

Obscuration of visual axis still remains the most frequent complication of pediatric cataract surgery with the most critical factor being the age at surgery. While opacification is nearly universal in infantile eyes, the incidence decreases with increasing age. Primary management of the posterior capsule and anterior vitrectomy are effective in preventing reopacification of visual pathways. The type and material of IOL also are very important factors affecting the incidence of VAO.

Glaucoma

Glaucoma is a recognized complication of pediatric cataract surgery. Despite improved surgical techniques, the incidence of glaucoma following successful cataract removal remains high. The most common type of glaucoma that develops following congenital cataract surgery is open-angle glaucoma. The risk factors include age at the time of surgery, pre-existing ocular abnormalities, type of cataract and the effect of lens particles, lens proteins, inflammatory cells and retained lens material. In addition, microcornea, secondary surgery, chronic postoperative inflammation, the type of lensectomy procedure or instrumentation used, pupillary block and the duration of postoperative observation have been found to influence the likelihood of glaucoma after pediatric cataract surgery. Patients who have undergone congenital cataract surgery should be monitored for glaucoma throughout their lives.

Uveal Inflammation

Intense uveal inflammation or severe fibrinoid reaction is a concern particularly in infants and young children. In our opinion, a traumatic surgical technique and ciliary sulcus, or asymmetrical fixation of IOL are other contributing factors which may be responsible for producing an exaggerated inflammatory response.

Other Complications

Retinal detachment and cystoid macular edema are infrequent following aphakia in pediatric cataract surgery. The reasons for this low incidence of postoperative retinal complications are not very well-known. Corneal astigmatism is recognized as a problem arising from cataract surgery. Postoperative astigmatism is more important in children than in adults because of its adverse effect on vision development and the risk of amblyopia.

MORE ON THIS TOPIC

Praveen MR, Shah SK, Vasavada VA, et al. Triamcinolone-assisted vitrectomy in pediatric cataract surgery: intraoperative effectiveness and postoperative outcome. J AAPOS. 2010;14:340-4.

Rahi JS, Dezateaux C, British Congenital Cataract Interest Group. Measuring and interpreting the incidence of congenital ocular anomalies: lessons from a national study of congenital cataract in the UK. Invest Ophthal Vis Sci. 2001;42:1444-8.

Vasavada AR, Praveen MR, Tassignon MJ, et al. Posterior capsule management in congenital cataract surgery. J Cataract Refract Surg. 2011;37:173-93.

Vasavada AR, Vasavada SA, Bobrova N, et al. Outcomes of pediatric cataract surgery in anterior persistent fetal vasculature. Cataract Refract Surg. 2012;38:849-57.

Wilson ME, Trivedi RH. Pediatric Cataract Surgery: Techniques, Complications and Management. 2nd ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2014.

Chapter 47.7
Glaucoma
Kirti Singh, Savleen Kaur

Primary congenital open-angle glaucoma, often termed congenital or infantile glaucoma is the most common form of primary glaucoma in children. An inherited, developmental defect of trabecular meshwork and anterior chamber angle of the eye, the disease manifests subsequent to very high intraocular pressure (IOP). This entity was recognized by Hippocrates and referred to as *buphthalmos* (Greek for ox-eye).

INCIDENCE

A rare disease seen in 1 of 10,000 births, it involves both eyes in 65–80% cases. Having a male preponderance, it comprises less than 0.01% of ophthalmic patients, but accounts for an extremely large chunk of blind school population (2–15%). Almost 25% are diagnosed at birth, 60% present by 6 months and 80% by 1 year of age.

INHERITANCE

Majority of primary congenital glaucoma (PCG) cases are sporadic, 10% familial, the latter being transmitted as an autosomal recessive trait. Most PCG map to GLC3A locus on chromosome 2 (2p21). Till date three loci for PCG have been discovered: (1) GLC3A (2p21), (2) GLC3B (1p36), and (3) GLC3C (14q24.3) and two candidate genes, *CYPB1* and *LTBP2* have been implicated. Various distinct mutations were identified in the coding region of *CYPB1* in patients of PCG-affected families. The chance of a second child having the disease ranges from 3% to 25% depending on number of siblings afflicted.

PATHOGENESIS

Cornea is the outermost layer of anterior part of eye. Maintenance of corneal clarity (transparency) and curvature is of utmost importance for proper refraction and passage of light rays, both events being crucial for vision. Aqueous humor is the fluid which fills the space between iris and cornea known as anterior chamber **(Fig. 1)**. Secreted by ciliary body positioned behind the lens, aqueous provides nutrition to the avascular lens, cornea, and vascular iris in addition to maintaining IOP which in turn is required for preserving corneal curvature and firmness of ocular globe. Corneal endothelium, the posterior most layer of cornea, is constantly bathed by aqueous. Positive hydrostatic pressure constantly exerted by IOP propels fluid aqueous into corneal tissues. This would result in corneal swelling/edema and loss of refractive property but for the presence of a highly metabolically active Na-K-ATPase dependent pump situated in the single layered corneal endothelium. This pump constantly works to push fluid aqueous back into anterior chamber in order to keep corneal thickness and transparency constant. Increased IOP gradually overpowers this pump by damaging corneal endothelium. The resultant corneal edema distorts the orderly arrangement of corneal lamellae causing corneal haze and scattering of light rays leading to *diminution of vision* and *photophobia* (intolerance to light). In addition, the increased IOP stretches the elastic sclera of the neonate causing bulging and stretching of cornea, manifesting as *buphthalmos* (large globe with large corneal diameter). Diminution of vision, photophobia and large corneal diameter thus are the classical triad of sign/symptoms of PCG.

Normal outflow of aqueous occurs through angle of anterior chamber (area where curved cornea meets flat iris) **(Fig. 2)**. Angle
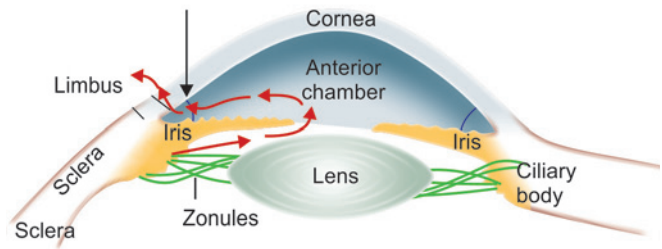
Figure 1 Anatomy of angle of anterior chamber. Red arrows depict aqueous pathway
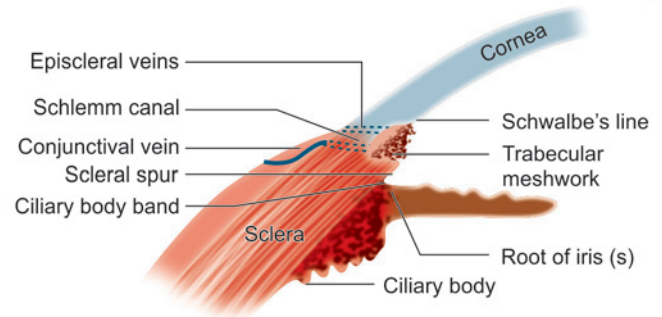
Figure 2 Angle of anterior chamber (in detail)

consisting of ciliary body, trabecular meshwork, and Schlemm's canal in sequence, serves to drain aqueous into subconjunctival blood vessels. In PCG, a developmental arrest of neural crest cell-derived anterior chamber angle tissue causes malformation and malfunctioning of angle with subsequent aqueous outflow obstruction. This aqueous impedance results in aqueous build up with subsequent rise in IOP. At molecular level, defect in myocilin protein (coded by *CYPB1*) present in trabecular tissue has been found to be the cause of this outflow dysregulation.

SECONDARY CONGENITAL/ DEVELOPMENTAL GLAUCOMA

Secondary congenital/developmental glaucoma (SDG) occurs in a plethora of conditions, details of which are beyond the purview of this chapter. A brief outline is given to make the pediatrician aware of these conditions that encompass many systems so that an ophthalmology referral in time prevents visual disability. For better understanding these disease entities are categorized according to the onset of manifestation.

Conditions Manifesting At Birth

Aniridia
We have discussed this condition in the previous chapters. Absence of iris causes uncontrolled light entry and subsequent photophobia. This photophobia is the most distressing feature and causes squeezing of eye when the child is subjected to light. Foveal/optic nerve hypoplasia, nystagmus, strabismus, microcornea and cataract coexist. Glaucoma occurs in 50–75% cases and manifests in late childhood or adolescence **(Figs 3A and B)**.

Sturge-Weber Syndrome
This phacomatosis manifests with unilateral (rarely bilateral) port wine stain of face due to cutaneous venous dilation in ophthalmic and maxillary division of trigeminal nerve. Leptomeningeal hemangiomas in occipital or temporal cortex are usually ipsilateral, associated with epilepsy, developmental delay, and mental
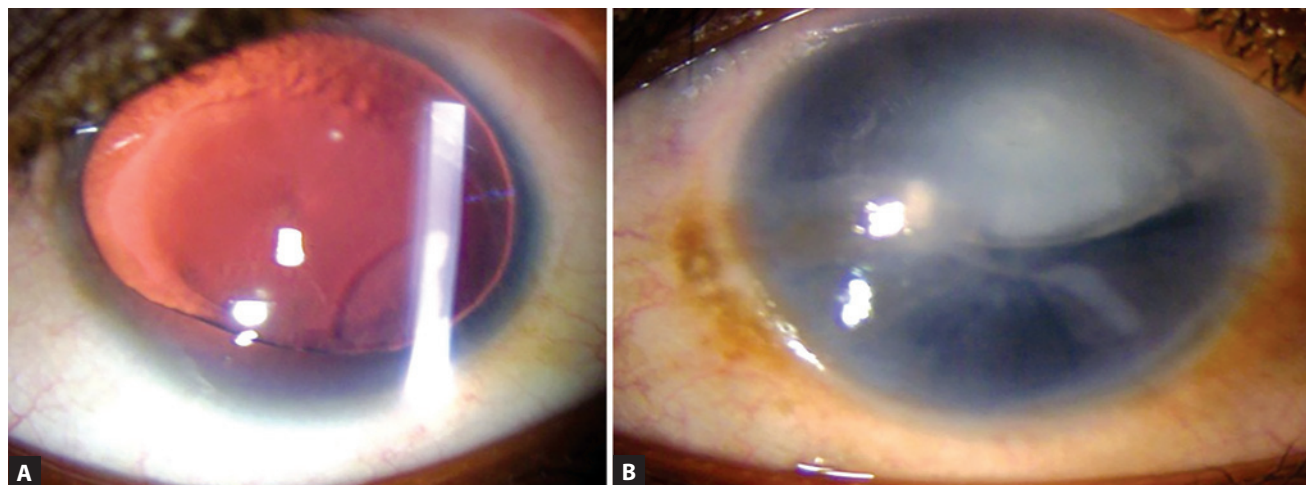
Figures 3A and B Aniridia with secondary glaucoma and cataract
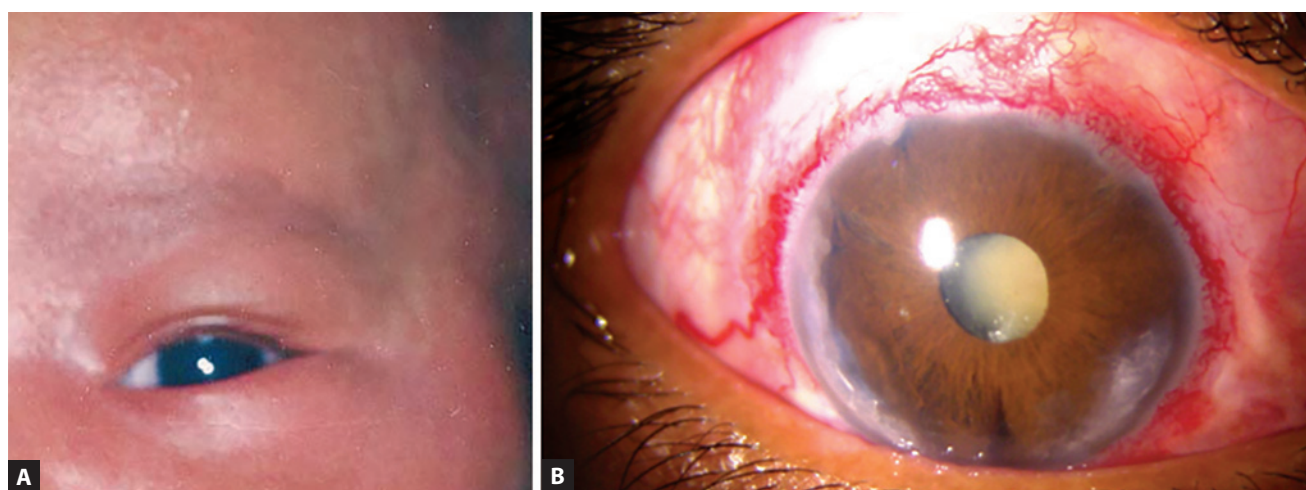
Figures 4A and B (A) Sturge-Weber syndrome with port wine stain; (B) Engorged dilated episcleral veins

retardation. Glaucoma seen in almost 30–70%, occurs in a very young child due to trabeculodysgenesis or in the older child due to raised episcleral venous pressure preventing aqueous outflow. Other associations are dilated episcleral veins **(Figs 4A and B)** and choroidal hemangiomas, the latter may result in hemorrhagic choroidal detachment during glaucoma filtering surgery.

Neurofibromatosis (von Recklinghausens Disease)

It is characterized by neurofibromas of skin, central and peripheral nervous system, iris, viscera, bony defects, specific pigmented skin lesions, the cafe-au-lait spots in the peripheral variant and bilateral acoustic schwannomas; the ocular features consist of yellow brown iris hamartomas (Lisch nodules). Chororetinal hamartomas may also be present. Glaucoma is associated in the peripheral variant and occurs when neurofibroma of ipsilateral eyelid is present **(Figs 5A and B)**. Debulking should not be attempted for neurofibromatosis.

Peters Anomaly

Defect in corneal development causes dense central corneal opacity, iris adhesions, and cataract at birth. Over a period of time glaucoma supervenes in 50% cases. The entity is usually unilateral, rarely bilateral and sporadic in occurrence. Systemic associations are: hearing defects, craniofacial dysostosis, cardiac and genitourinary abnormalities and spinal defects. Peters plus or Krause-Kivlin syndrome is association of the ocular anomaly with

short limbs, broad distal extremities and developmental delay. Management includes corneal transplantation for severe bilateral opacification along with amblyopia and glaucoma treatment. Glaucoma filtering/tube shunt surgery is often required as medical therapy proves to be inadequate in controlling the glaucoma. Visual prognosis remains poor and corneal grafting/keratoplasty is also required for Peters anomaly.

Conditions Manifesting Later (First-Second Decade)

Axenfeld-Rieger Anomaly

Abnormality in neural crest development leads to ocular, face bones, dental and pituitary gland defects. Rieger anomaly is the name reserved for ocular manifestations; Axenfeld prefix indicates associated systemic malformations. Manifesting within first two decades of life, secondary glaucoma occurs in 50% cases.

Ocular manifestations Prominent Schwalbes line on gonioscopy, iris hypoplasia (holes, corectopia, polycoria, ectropion uvea) are seen along with high refractive errors; and cataract/glaucoma complicated by amblyopia **(Figs 6A and B)**.

Systemic associations Maxillary hypoplasia, telecanthus, micrognathia, mandibular prognathism, dental defects (microdontia/peg like teeth, hypodontia, adontia), middle ear deafness, heart defects, mental deficiencies and empty sella syndrome.
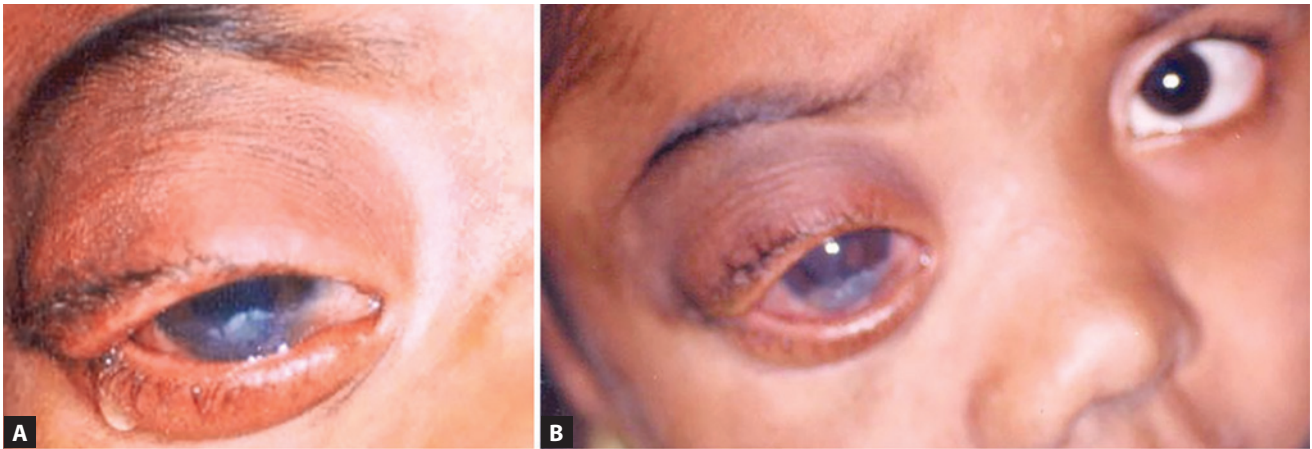
Figures 5A and B Neurofibromatosis with secondary glaucoma and exposure keratitis in a 5-year-old child

Figures 6A and B Axenfeld-Rieger syndrome. (A) Iris stromal thinning, corectopia; (B) Microdontia and hypodontia
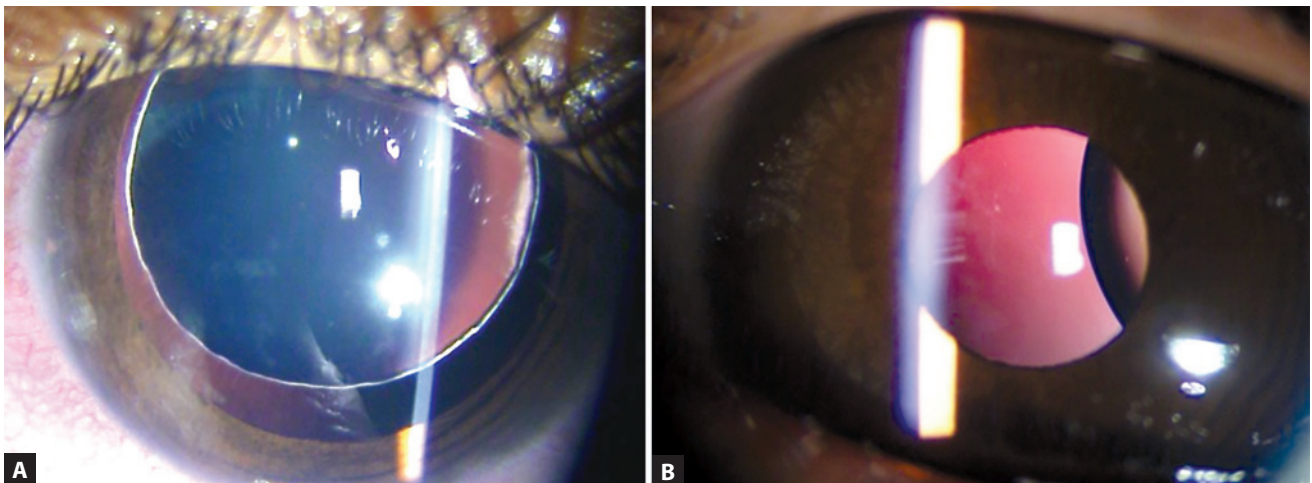
Figures 7A and B (A) Microspherophakia in Weill-Marchesani syndrome; (B) Subluxated lens in Marfan syndrome

Ectopia Lentis

Lens dislocation or subluxation occurs in Marfan syndrome, homocystinuria, microspherophakia **(Figs 7A and B)**. It causes glaucoma by inducing pupil block. IOP is high with corneal edema. Surgical extraction of the truant lens must be performed once IOP is medically controlled. Child maybe left aphakic and rehabilitated with contact lenses. Definitive IOL placement by special scleral fixation technique if required is deferred until child reaches adulthood.

Pseudophakic/Aphakic Glaucoma

This occurs in children who have undergone congenital cataract surgery. Glaucoma incidence increases with time elapsed since surgery and ranges from 6% and 25%. The risk factors identified for glaucoma development are sulcus fixated IOL, protracted surgical trauma, and chronic inflammation. Lifelong follow-up is needed to screen for glaucoma in children operated for cataract. Medical management is with beta blockers and carbonic anhydrase inhibitors. Miotics are often extremely useful but alpha agonists

are contraindicated in young children due to their propensity to cause respiratory depression and sleep apnea. Glaucoma filtering surgery is ultimately needed.

Uveitic Glaucoma

Sign of iridocyclitis range from aqueous flare, cells, keratic precipitates, muddy iris, posterior and peripheral anterior synechiae (PAS). Iris atrophy of varying grades is a clue to prior episodes of iridocyclitis. Uveitis is a characteristic feature of juvenile idiopathic arthritis.

Incidence of glaucoma in these children ranges from 14% to 27% and has a poor prognostication. In addition chronic requirement of topical steroids exacerbates the glaucoma. Steroid usage must thus be limited to topical pulse steroid therapy to control acute exacerbations and never for elimination of aqueous flare.

Iatrogenic/Acquired Glaucoma

Steroid induced glaucoma Widespread and unregulated steroid use for nonspecific ocular symptoms is the bane of Indian subcontinent. Steroids stabilize lysosomal membrane and reduce their catabolic effect on glycosaminoglycans. By inhibiting phagocytosis of trabecular endothelial cells aqueous outflow pathway resistance is increased and propensity for glaucoma is unmasked. Such children develop high IOP which is asymptomatic and painless along with concomitant cataract due to persistent use of topical steroid eye drops. Topical steroids have a greater propensity for IOP rise than systemic usage. The IOP enhancing effects are proportional to the anti-inflammatory potency and dosage of steroid preparations. Concomitant cataract due to steroid abuse is often associated. Discontinuation of steroids is often the solution and if not possible, substitution with a nonsteroidal noninflammatory drug is the answer. *Constant monitoring of IOP is must for children on steroid drops.*

Traumatic glaucoma Usual history is of a fall or blunt trauma with a racket, ball, shuttlecock or fist. Blunt injuries may result in glaucoma because of continuing inflammation, hyphema with or without angle recession, traumatic iridocyclitis, or lens dislocation or rupture. *Angle recession glaucoma* occurs subsequent to a tear in ciliary muscles with subsequent fibrosis and impaired outflow ability of trabecular meshwork. Gonioscopy is diagnostic and reveals irregular widening of ciliary body band which has a slate gray appearance. Incidence of angle recession in traumatic hyphema is high (55–70%), however incidence of glaucoma varies from 4% to 20%. The IOP rise occurs as early as few months and

as late as 40 years after injury. Topical β-blockers, adrenergic agents and carbonic anhydrase inhibitors are the drugs commonly used to control the IOP. Use of systemic acetazolamide is contraindicated in sickle cell disease patients as this drug is known to cause metabolic acidosis thereby increasing sickling of the RBC in anterior chamber. Indications for surgical drainage are—IOP of more than 50 mm Hg for 5 days, more than 35 mm Hg for 7 days, total *eight ball* hyphema not resolving for 9 days, or early signs of corneal blood staining. Surgical drainage is accomplished by simple paracentesis, washout of anterior chamber, viscoexpression of clot or automated extraction.

Chemical burn Glaucoma can occur both in the acute and late setting. Alkali burn patients have a greater propensity to develop secondary glaucoma. *In acute stage*, collagen shortening, anterior chamber inflammation and shrinkage cause a variable IOP response. IOP elevation occurs in a bimodal pattern. An initial rise due to collagen fibril hydration, longitudinal shortening of collagen fibers and distortion of angle is followed with a second rise within a few hours. The second spike is due to obstruction of outflow channels by increased episcleral pressure, prostaglandin mediated inflammatory trabeculitis and uveitis. In the *healing phase* depending on the extent of burn, the IOP varies. It is balanced by decreased aqueous secretion due to ciliary body damage versus continued conjunctival scarring/shrinkage attributed to obstructed outflow pathway. Development of PAS, fibrous ingrowth, and increase in episcleral pressure contribute to glaucoma **(Figs 8A and B)**.

The focus is on reducing the chemical insult by copious wash and decreasing inflammation by judicious use of corticosteroids. Wash must be done immediately and intensively for 20–30 minutes. Glaucoma is managed by aqueous suppressants. Miotics and prostamides may increase intraocular inflammation, and thus are best avoided. The prognosis for such patients is often poor but timely trabeculectomy can save the eye if performed once the active phase has resolved. Symblepharon with subsequent fornix shortening may prevent trabeculectomy or tube shunt from being performed, in such situations laser cyclophotocoagulation remains the only option.

Retinopathy of prematurity (ROP) The glaucoma presents at 3–6 months of age once the cicatricial phase starts. Contracture of retrolental mass causes anterior chamber (AC) shallowing and angle closure glaucoma. The child presents with nausea, vomiting and is often misdiagnosed as a gastric episode. The cornea in these children is small, steep, with a convex iris and shallow
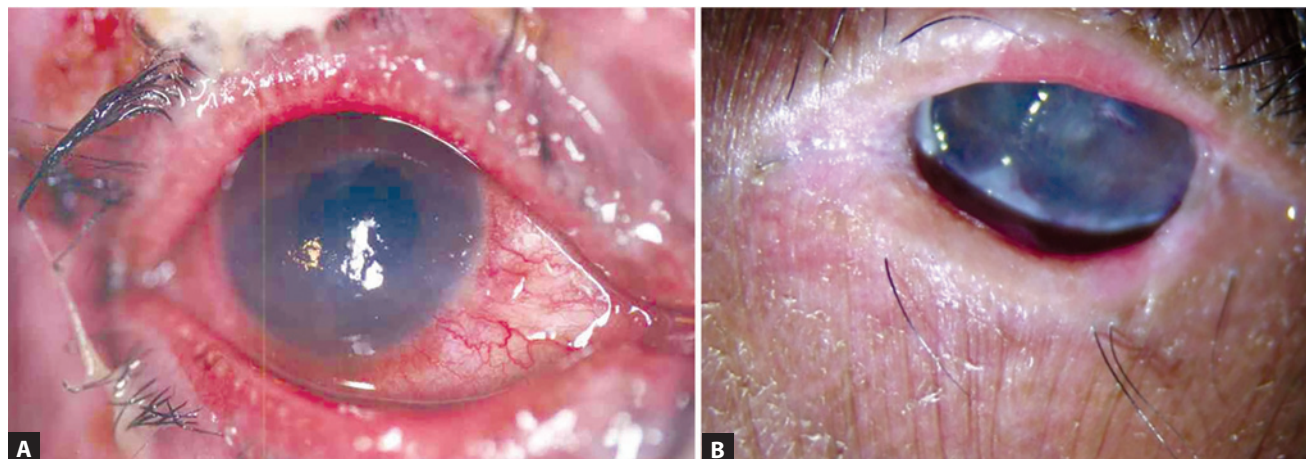
Figures 8A and B (A) Lid distortion; corneal haze after acute chemical burn; (B) Symblepharon, ankyloblepharon, persisting corneal haze with cataract and secondary glaucoma

Table 1 Causes of epiphora in an infant

	Congenital glaucoma	Congenital nasolacrimal obstruction	Ophthalmia neonatorum	Keratomalacia
Corneal diameter	Enlarged	Normal	Normal	Normal
Corneal clarity	Deranged, hazy cornea	Normal	If active ulcer then haze	Very hazy, melting of cornea
Discharge	Watery	Purulent, sticking of eyelids	Very purulent, fused eyelids	Variable
Regurgitation test	Negative	Positive	Negative	Negative
Photophobia	Present	Negative	Present	Positive/negative
Treatment	Surgical	Sac massage, if fails then probing and syringing	Intensive topical antibiotic therapy	Treat malnutrition and Vitamin A therapy
Systemic examination	Healthy	Healthy	Irritable child	Malnourished child

anterior chamber. Continued contraction of retrolental membrane may cause a spontaneous deepening of anterior chamber and resolution of glaucoma. Constant vigilance is needed as glaucoma can intervene at any stage later on in life.

Treatment—Medical therapy is often ineffective. A large peripheral iridectomy is warranted as smaller PI often close. A prophylactic PI in severe ROP with shallow anterior chamber is now recommended.

PRIMARY CONGENITAL GLAUCOMA

Congenital glaucoma is usually detected by parents/care giver in three forms. The most severe manifestation is in form of diffuse corneal haze due to edema. Corneal edema causes scattering of light with resultant photopia (intolerance to normal light). The baby becomes extremely sensitive to light and classically burrows his face in bedclothes or pillow on light exposure. This is accompanied by excessive reflex tearing. Since tear secretion does not occur at birth, tearing may not always be present. Significant IOP elevation occurs, but sometimes globe enlargement and limbal stretching mask the IOP rise. The child may present with one or more features of the classic triad—epiphora, photophobia and blepharospasm. The severity of presenting signs differs in infants depending upon the magnitude and duration of IOP elevation. It is important for the pediatrician to differentiate it from other causes of epiphora (excessive tearing) **(Table 1)**.

Clinical Examination

Systemic associations are seen in secondary glaucoma and not in primary glaucoma. The pediatrician should rule out the other causes of corneal haze, epiphora and photophobia including mucopolysaccharidosis, inclusion conjunctivitis, ophthalmia neonatorum and head trauma by traumatic forceps delivery.

Visual Acuity
The enlargement of globe causes a myopic shift which in turn leads to amblyopia if significant anisometropia is present. Haab's striae **(Fig. 9)** may produce significant astigmatism. Children between 3 years and 10 years of age with elevated IOP may develop progressive myopia and astigmatism, due to continued scleral stretching.

Cornea
A corneal diameter of more than 12 mm or asymmetry in corneal diameter between two corneas in the first year of life is a highly suspect finding. The neonatal eye is distensible and stretches on elevation of IOP, leading to enlargement of cornea and limbus. This high IOP causes pressure upon lamina cribrosa (sieve like structure at posterior part of sclera through which optic nerve fibers exit) and causes its posterior bowing which manifest as cupping of disc and causes pressure atrophy of optic nerve. Often, in early stages underlying breaks in Descemets membrane may be seen while in advanced cases opacification of corneal stroma persists along with linear breaks. These tears in Descemets membrane (Haabs striae)
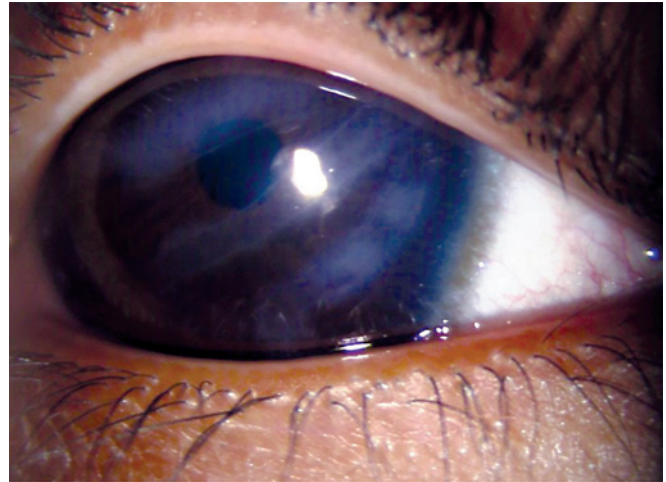
Figure 9 Haab's striae due to congenital glaucoma, are concentric to limbus

are classical and occur in 20% children with primary glaucoma at birth and in more than 60% of those diagnosed at 6 months age. To differentiate these breaks from those induced by forceps delivery, it must be remembered that Haabs striae due to congenital glaucoma are concentric to limbus, multiple and associated with limbal stretching and increased IOP. They may or may not be unilateral. Those due to trauma are always unilateral, associated with corneal haze, vertical in orientation, and not associated with limbal stretching nor with increased IOP.

Ocular Examination and Tonometry
Intraocular pressure measurement in an infant or child is difficult and traumatizing to the child. Useful handheld devices like Perkins, Tono-Pen and I-Care tonometers can be used in kids older than 3 years (without nystagmus). In older children Goldmann applanation tonometry can be done. Tonometry is usually performed under general anesthesia as a prelude to definitive surgery. For follow-up, examination under anesthesia is preferred but examination of the small child can be undertaken by immobilizing the child's head and hand in the manner depicted in **Figures 10A and B**. Detailed discussion on technique of examination under anesthesia is beyond the scope of this chapter. The child is subjected to examination of anterior chamber, gonioscopy, and complete retinal examination using appropriate techniques, by an ophthalmologist. Few obvious findings are shown in **Figures 11A and C**. Fundoscopy findings are depicted in **Figures 12A and B**.

Management
Definitive treatment modality for primary infantile glaucoma is surgical intervention, medications play an adjunctive role only.

Figures 10A and B (A) Technique of examination of child's eye in OPD; (B) Corneal haze with enlarged cornea visible
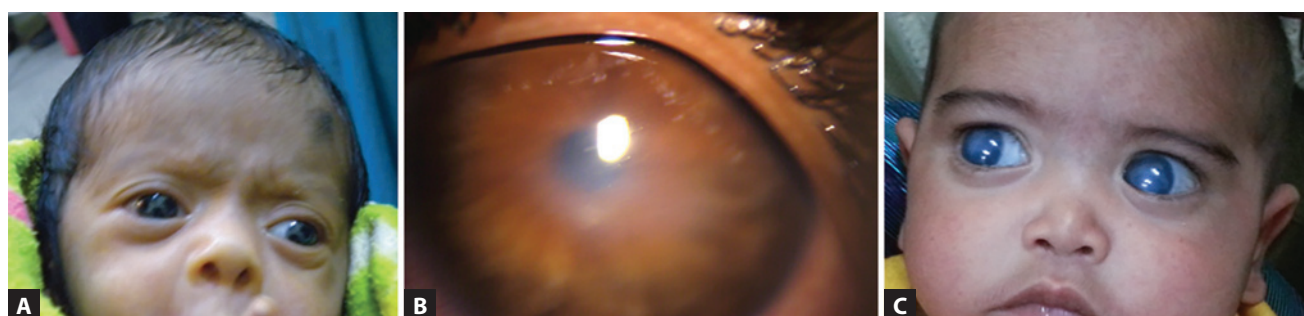
Figures 11A to C (A) Enlarged globe, clarity maintained, limbal stretching present. Bilateral buphthalmos with minimal corneal haze; and (B) Significant haze; (C) Persisting despite successful glaucoma surgery
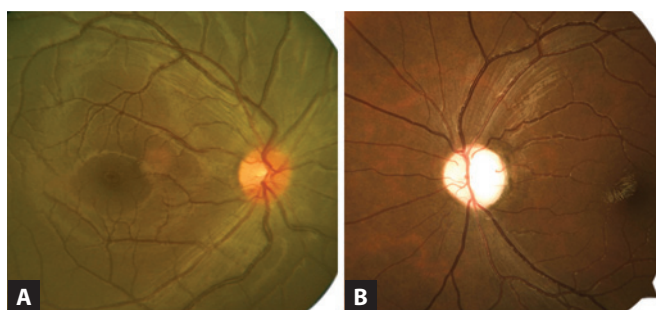
Figures 12A and B (A) Fundus photo of normal optic nerve head with no cup, pink neuroretinal rim (NRR); (B) Fundus photo of buphthalmic child, optic nerve head with large cup, absent NRR

Medical therapy is used preoperatively, to help clear the cornea for angle surgery; as a temporary measure, when the infant is unstable for general anesthesia; and as an adjunctive modality for postoperative high IOP. Timolol 0.25% (a beta-blocker), dorzolamide 2% (topical carbonic anhydrase inhibitor), or systemic acetazolamide can be used for medical management. Angle surgery should be attempted as the initial procedure in clear cornea as it spares the limbus for a future procedure. Goniotomy is the surgery performed using a special Barkans lens to visualize the angle and the abnormal angle is incised with a goniotomy knife. Trabeculotomy is the preferred surgery once corneal opacification has occurred or once two goniotomies have failed. Combined trabeculotomy—trabeculectomy is performed in failed previous angle surgery (≥ 2 goniotomies), and is the initial surgery in children younger than 5 years.

Long-term Follow-up

Control of IOP is only one challenge in treating children with primary infantile glaucoma; visual loss may occur not only from corneal scarring and optic nerve damage but also as a result of amblyopia related to anisometropia or strabismus, or both. These have to be treated concomitantly. Lifetime follow-up is required despite IOP control. Target IOP in lower 20s may be adequate in a child with healthy optic discs and stable refraction but others with more severe disease may progress on the same IOP and require lower target IOP.

MORE ON THIS TOPIC

Alodhayb S, Morales J, Edward DP, Abu-Amero KK. Update on pediatric glaucoma. Semin Ophthalmol. 2013;28:131-43.

Courtright P, Hutchinson AK, Lewallen S. Visual impairment in children in middle- and lower-income countries. Arch Dis Child. 2011;96:1129-34.

Khan AO. Conditions that can be mistaken as early childhood glaucoma. Ophthalmic Genet. 2011;32:129-37.

Khan AO. Genetics of primary glaucoma. Curr Opin Ophthalmol. 2011;22:347-55.

Moore DB, Tomkins O, Ben-Zion I. A review of primary congenital glaucoma in the developing world. Surv Ophthalmol. 2013;58:278-85.

Olitsky SE. Primary infantile glaucoma. Int Ophthalmol Clin. 2010;50:57-66.

Chapter 47.8
Optic Nerve and Pupil
Digvijay Singh, Pradeep Sharma

Infancy and early childhood is the formative period for development of vision and the cortex in relation to the visual system. Unlike other parts of the eye, cortical visual system continues to develop until late into the first decade and continuous changes have been seen at older ages too. There is significant plasticity of visual cortex and though development tends to significantly reduce after first decade, often there have been central visual changes noted in early teens such as improvement of amblyopia by occlusion therapy or development of alternate visual pathways after optic neuritis. This chapter focuses on the neuro-ophthalmological aspect of visual system and covers issues related to pupil and its abnormalities in that context.

DEVELOPMENTAL ANOMALIES OF THE OPTIC NERVE

Optic disc is a well-defined circular/slightly vertically oval structure in the fundus with a well-defined cup and a healthy pink neuroretinal rim surrounding it. The central retinal artery and vein emerge through the disc as they enter the retina **(Fig. 1)**. The disc is about 1.5 mm in diameter.

Optic Nerve Hypoplasia

Resulting from an insult during first trimester of pregnancy, it is seen either as a complete hypoplasia or in a segmental form in children of mothers with insulin dependent diabetes. The disc is small, pale within a normal optic canal giving rise to a double ring sign **(Fig. 2)**. Optic nerve hypoplasia is associated with midline defects including the corpus callosum agenesis, absence of septum pellucidum, etc. Septo-optic dysplasia (de Morsier syndrome) refers to optic nerve hypoplasia along with underdeveloped hypothalamus and pituitary resulting in growth hormone deficiency, neonatal seizures, diabetes insipidus and hyperprolactinemia. Optic nerve hypoplasia presents with vision loss and may be unilateral or bilateral, often associated with squint and amblyopia. While there is no treatment for optic nerve hypoplasia, correction of amblyopia using occlusion therapy should be tried. Magnetic resonance imaging (MRI) should be ordered in cases of optic nerve hypoplasia to rule out midline defects.

Optic Nerve Aplasia

Total absence of optic nerve head, is a very rare occurrence. The child will present with unilateral or very rarely bilateral complete visual loss and the absence of any structure resembling the optic nerve head on fundus examination.

Myelinated Nerve Fibers

Normally, the myelination stops at the lamina cribrosa, however if the myelination continues onto the retinal nerve fibers beyond the disc, it is visible on fundoscopy and labeled as myelinated nerve fibers **(Fig. 3)**. They appear as white feathery fibers in the retina around the disc oriented in same manner as normal retinal nerve fibers. They may be asymptomatic presenting with only an enlarged blind spot or could be associated with vision loss if they involve the macula. No specific therapy is indicated.

Morning Glory Disc Anomaly

Abnormal closure of embryonic fissure or maldevelopment of distal optic stalk leads to this abnormality of the optic nerve head and retina. The optic disc and surrounding retina are excavated in funnel shaped morphology along with increased number of abnormally branching vessels emanating out from them **(Fig. 4)**. This resembles the appearance of a morning glory flower and the excavation is covered with white glial tissue. The visual acuity of such eyes is variable but usually around 20/200 (Snellen visual acuity). The anomaly is associated with midfacial anomalies, basal encephalocele and also may be associated with Moyamoya disease.

Tilted Disc Syndrome

This implies a horizontally oval/oblique disc or a vertically tilted disc with an elevated superior pole and a depressed inferior pole **(Fig. 5)**. Associated myopic degeneration and astigmatism are common findings. Visual field defect frequently seen is a bitemporal hemianopia not respecting vertical meridian unlike
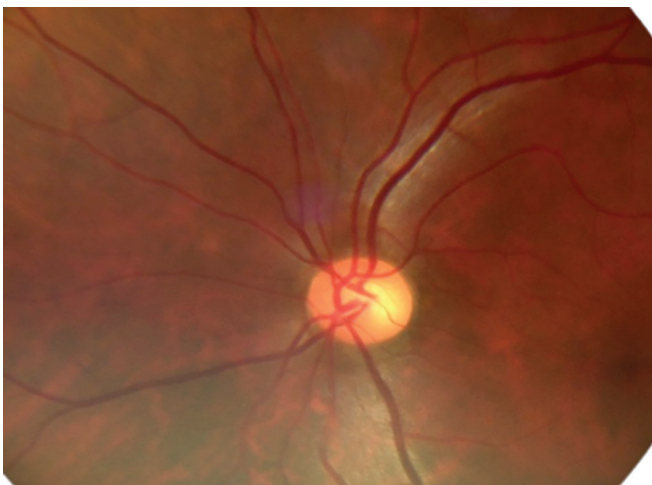
Figure 1 Normal optic disc. Disc margins are distinct, there is a central cup with a healthy pink neuroretinal rim around it with cup disc ratio of 0.3
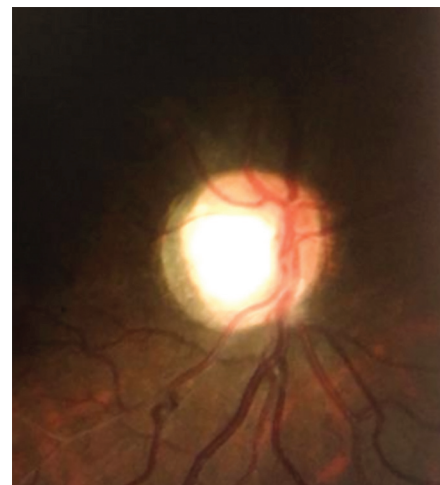
Figure 2 Optic nerve hypoplasia. Optic nerve is small and pale appearing along with scleral rim showing in form of a classical double ring sign

Figure 3 Myelinated nerve fibers. Feathery fluffy white fibers emanating from optic disc
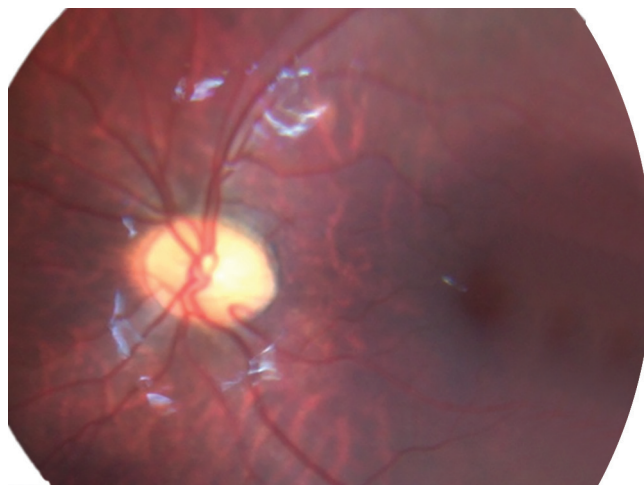
Figure 5 Tilted optic disc. Horizontally oval optic disc. This photograph is taken using the smartscope portable fundus camera
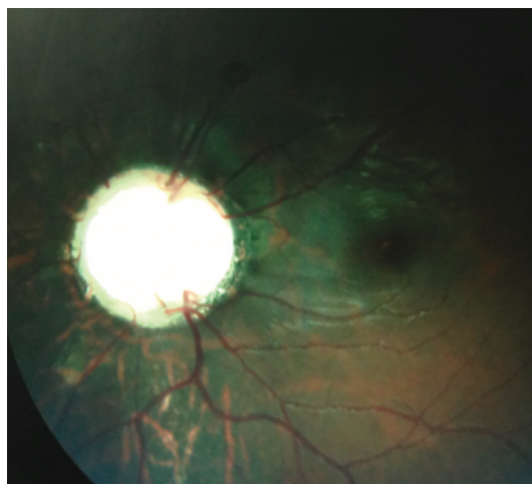
Figure 4 Morning glory syndrome. Large disc with a central funnel shaped excavation and multiple abnormally branching vessels emerging out
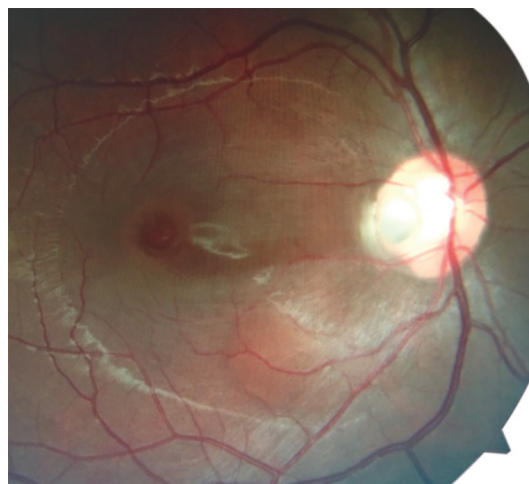
Figure 6 Optic disc pit in inferotemporal location with central serous retinal detachment. Such cases are often asymptomatic till macula is elevated with fluid

a pituitary adenoma. Correction of refractive error often corrects the field defect. Congenital stationary night blindness may be coexistent.

Optic Disc Pit

These are shallow or deep holes/pits, usually in the inferotemporal quadrant of the disc, often associated with a serous retinal detachment **(Fig. 6)**. They may present at any age group and are asymptomatic until serous retinal detachment develops, in which case they will present as reduced vision. While there is no treatment to correct the optic disc pit, localized laser of retina may be done to curtail fluid leakage and prevent serous retinal detachment.

HEREDITARY OPTIC NEUROPATHY/ATROPHY

These present in first decade of life with progressive vision loss and optic atrophy. Majority are autosomal dominant in inheritance and are classified as dominant optic atrophy, others are autosomal recessive or mitochondrial. Clinical feature of this group of disorders constitutes vision loss, ranging from light perception to near normal, which progressively deteriorates with passage of time. The vision loss may present in a subacute manner, particularly in

the second decade. Primary optic atrophy, manifesting as pale yellow-white optic disc with reduced small vessels, well-defined cup and margin is the hallmark **(Fig. 7)**. There is no specific treatment at present.

Wolfram syndrome is an optic atrophy of a severe nature with poor prognosis. It is also called DIDMOAD syndrome referring to a conglomerate of Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness. Other associations may include anosmia, ataxia, seizures, mental retardation and altered CSF proteins. Lebers hereditary optic neuropathy (LHON) occurs during adolescent age and has a mitochondrial inheritance. The visual acuity is around 20/200 and central or centrocecal scotomas are common. No specific treatment exists.

OPTIC NEURITIS

Optic neuritis refers to inflammation of the optic nerve often in association with a demyelinating illness. It is of two forms, *retrobulbar neuritis* or *papillitis*. Nearly two-thirds have papillitis and are bilateral. Nearly three-fourths of optic neuritis in children is preceded by a febrile illness, often viral exanthema. The overall prognosis for optic neuritis in children is poor than that for adults but unilateral cases tend to fare better than bilateral ones.
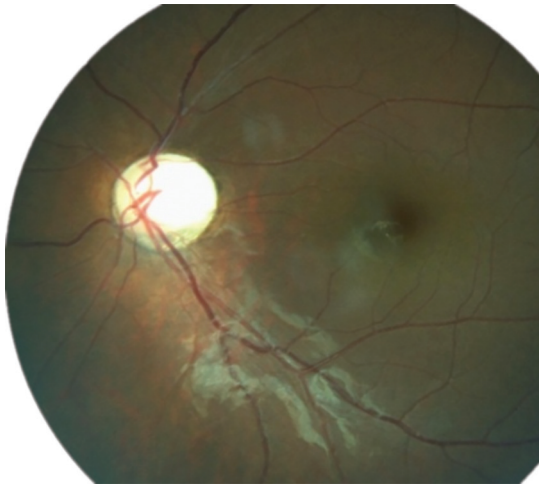
Figure 7 Primary optic atrophy. The optic disc is diffusely pale looking with distinct margins and preserved cupping. Number of small vessels seen on the disc is reduced. Such atrophy is seen in hereditary optic neuropathies

Optic neuritis in India differs from West. In the authors' experience, the mean age of optic neuritis in India is around 12 years with an equal male-female preponderance. Only half the patients recover visual acuity of 20/60 or better and nearly a fifth develop recurrence of optic neuritis. The conversion into multiple sclerosis is seen in 10% of the cases.

When to Suspect

Optic neuritis should be suspected if there is a subacute vision loss in one or both eyes in presence of a relative afferent pupillary defect in unilateral or asymmetric bilateral cases. The vision loss may be associated with retro-ocular pain on eye movements. The fundus may be normal (retrobulbar neuritis) or show a mildly swollen hyperemic disc (papillitis) **(Fig. 8)**. This clinical picture within 2 weeks of a febrile illness helps to strengthen the suspicion. Management involves evaluating visual functions like visual acuity, color vision, contrast sensitivity and visual fields. Visual evoked responses show reduced amplitude and delayed latency. If there is any sign of infection, it should be treated and intravenous pulse steroids (methyl prednisolone) may be given under cover of antibiotics. Follow-up of such patients is important in view of

development of any neurological deficits suggestive of multiple sclerosis. For diagnosing optic neuritis associated with multiple sclerosis, investigation of choice is a contrast enhanced MRI of head and orbit.

A special form of optic neuritis, known as neuroretinitis maybe seen in children where there is a papillitis along with exudates on the macula presenting as a *macular star*. Such cases occur as a result of infection and should be managed accordingly and do not routinely require corticosteroids **(Fig. 9)**.

PAPILLEDEMA

Papilledema is used for a disc edema secondary to raised intracranial pressure. This may in turn be due to an intracranial space occupying lesion or hydrocephalus or pseudotumor cerebri. The predominant clinical features of papilledema are transient obscuration of vision or a permanent vision loss, enlarged blind spot or constricted visual fields on perimetry and an association with headache in presence of bilateral swollen discs. The swollen discs may have associated peripapillary hemorrhages and exudates on macula forming a macular fan **(Fig. 10)**. A papilledema like picture is also seen in malignant or accelerated hypertension and hypertensive/diabetic papillopathy. Papilledema warrants an urgent evaluation for cause of raised intracranial tension.

Pseudopapilledema is a condition where the discs are not actually swollen but appear to be so due to disc drusen, high hypermetropic refractive error or leukemic infiltrates. It is differentiated from true papilledema by absence of a raised disc or absence of tell-tale signs of papilledema such as macular exudates or receding fluid lines/Paton lines.

ACQUIRED OPTIC ATROPHY

In early infancy, optic atrophy is often the result of hypoxia and associated with hypoxic ischemic encephalopathy. Confirmatory evidence is periventricular leukomalacia on MRI. Other causes in early childhood include atrophy secondary to optic nerve glioma and thus the presence of a unilateral optic atrophy or unilateral nystagmus should alert the physician to look for this condition. In later childhood, craniopharyngiomas and retinal degenerative disorders may lead to bilateral optic atrophy. Optic atrophy of a secondary appearance (dirty gray colored disc with blurred margins and obscured cup) may result from hydrocephalus, pseudotumor cerebri or an intracranial space occupying lesion **(Fig. 11)**. Optic

Figure 8 Papillitis in optic neuritis showing hyperemic disc with slightly blurred margins
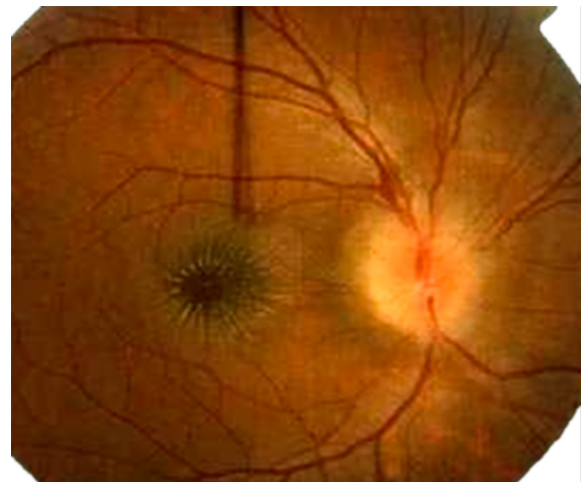
Figure 9 *Neuroretinitis:* Hyperemic disc with blurred disc margins and exudates on macula forming a macular star
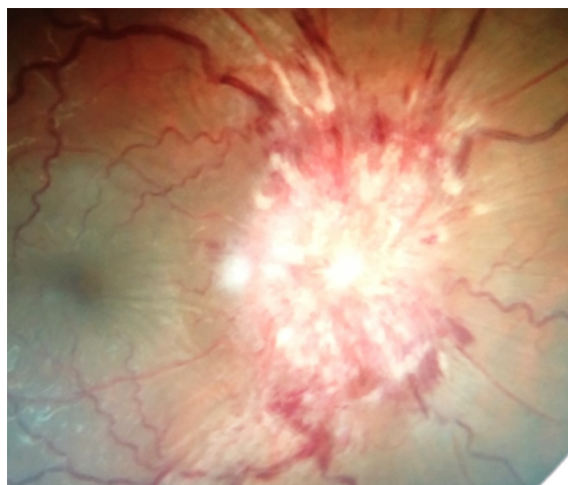
Figure 10 *Papilledema:* Swollen disc, peripapillary hemorrhages and exudates in vicinity

Figure 11 *Secondary optic atrophy:* Dirty looking disc, blurred margins and obscured cups

atrophy of either a primary appearance (as described for hereditary neuropathies) may appear after retrobulbar neuritis or a secondary appearance may develop after papillitis. **Table 1** shows various causes of optic atrophy based on age.

CORTICAL VISUAL IMPAIRMENT

These infants or children have normal ocular structures, normal pupillary reactions and normal fundus with significant vision loss implying cortical cause of vision impairment. The only definite abnormality seen in such cases would be an abnormal visual evoked response and changes on MRI. Cortical visual impairment is often congenital as in occipital porencephaly, intrauterine infections, optic radiations abnormalities or hypoxic ischemic encephalopathy. Cortical vision loss could also be acquired due to embolic infarcts, blocked shunts or trauma. There is a great difficulty in prognosticating cases with cortical blindness and generally those with no changes on the MRI tend to fare better than

those with florid changes. Considering general inattentiveness of children, and normal ocular examination, it is difficult to diagnose these cases. Treatment is not very helpful.

Hysterical vision loss may also be seen in children particularly after an acute stress and needs to be differentiated from malingering which a child may do just as part of an attention seeking behavior. Essentially, hysterical vision loss occurs outside the patient's conscious awareness unlike malingering which is purposeful. It is a diagnosis of exclusion and needs to be differentiated from organic causes of vision loss which may have a normal fundus such as occult macular dystrophies (Stargardt's dystrophy, rod monochromatism, isolated foveal aplasia, etc.), retrobulbar neuritis, Leber's congenital amaurosis, retinitis pigmentosa sine pigmento, and drug toxicity.

PUPILLARY ABNORMALITIES

Developmental Anomalies

Congenital Miosis/Microcoria
This condition, due to underdevelopment of dilator pupillae muscle, manifests with unilateral or bilateral small pupil (< 2 mm diameter) which responds poorly to mydriatic drops. Treatment involves a surgical pupilloplasty.

Congenital Mydriasis
Presenting with bilateral fixed dilated pupils, it is called as *familial iridoplegia*. The diagnosis is made after ruling out use of any pharmacological agent, trauma or neurological illness.

Corectopia
Displacement of pupil from its normal position of about 0.5 mm inferonasally to the center of the iris is called corectopia. It often coexists with colobomas, subluxated lens or anterior segment dysgenesis. The pupil may be slit like and dilates poorly.

Polycoria
This refers to multiple pupils in the iris each having its own sphincter and occurs in anterior segment dysgenesis syndromes.

Afferent Pupillary Abnormalities
Amaurotic pupil refers to the pupil of a blind eye where there is no direct reaction on shining light into the blind eye but an intact consensual and near reflex.

Table 1 Causes of disc pallor in relation to age of presentation

Age group	Causes for disc pallor
Children	Hereditary optic neuropathies (AD/AR/XL), nutritional deficiency neuropathy, atrophy associated with CNS disorders, atypical optic neuritis, Schilder's disease, hypoxic ischemic syndrome (antenatal, perinatal and postnatal), optic nerve glioma, secondary to papilledema (hydrocephalus, osteopetrosis) and metabolic disorders (methylglutaconic aciduria, ceroid lipofuscinosis)
Adolescents	Leber's hereditary optic neuropathy, atypical optic neuritis, multiple sclerosis, neuromyelitis optica, toxic optic neuropathy, pituitary adenoma, tapetoretinal degeneration and associated with systemic/CNS disorders
Young adults	Optic neuritis and multiple sclerosis, toxic optic neuropathy, traumatic neuropathy, meningioma, associated with systemic disorders (neurosyphilis, tuberculosis, toxoplasmosis, diabetes mellitus, HIV) and associated with CNS disorders (raised ICP, spinocerebellar ataxia, Friedreich ataxia, encephalitis, encephalopathy, meningitis, SSPE, Guillain-Barré syndrome, etc.)

Abbreviations: CNS, central nervous system; SSPE, subacute sclerosing panencephalitis; ICP, intracranial pressure; HIV, human immunodeficiency virus.

Common Eye Abnormalities
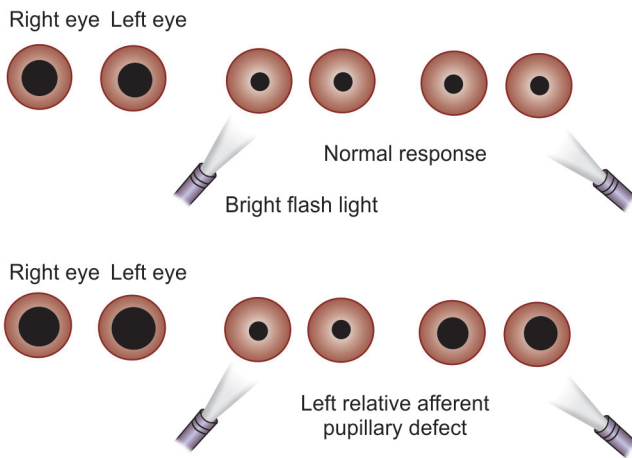
Figure 12 Swinging flashlight test demonstrating a left relative afferent pupillary defect. In diagrams in first row, note how swinging the flashlight from one eye to other results in constant constriction of two pupils, while in the row below, pupils dilate when flashlight is swung from right eye to left eye. This indicates a left relative afferent pupillary defect

Marcus Gunn Pupil

This refers to the relative afferent pupillary defect seen in eyes having a neuro-ophthalmic disorder. Here, the direct reflex of the affected eye is poorer than the consensual reflex incited by stimulating the normal eye. This is best elicited using *swinging flashlight test*. The swinging flashlight test requires use of a bright flashlight and a dimly lit room. The patient is asked to look at a far distance object in the room while a flashlight is rapidly swung illuminating one eye followed by the other. When the flashlight is shone on eye, say right eye, then pupil of that eye will constrict (direct response) as will the pupil of fellow eye, in this case left eye (consensual response). When the flashlight is rapidly swung and shone on left eye, normally, pupil will remain constricted again (direct response) while right eye pupil will also remain constricted (consensual response). If optic nerve in left eye was damaged, when flashlight will swing onto left eye, left pupil would dilate (left relative afferent pupillary defect) as will the right eye pupil. If the flashlight is now swung back onto right eye, both pupils will constrict again due to an intact afferent pathway of right eye. This confirms the left relative afferent pupillary defect or left Marcus Gunn pupil **(Fig. 12)**.

Efferent Pupillary Abnormalities

Argyll-Robertson Pupil

This is a form of light near dissociation seen specifically in tertiary syphilis or lesions of dorsal midbrain. The pupils are small, irregular and react briskly to a near target and sluggishly to light.

Figure 13 Horner syndrome. Notice right eye is appearing enophthalmic with a ptotic lid and miosis of right pupil

Adie Pupil

A rare form of efferent pupillary abnormality, Adie's pupil is mostly idiopathic but may be associated with varicella infection or measles vaccination. The child is asymptomatic or complains of near vision difficulty. Often unilateral, it is picked up when a parent notices anisocoria (affected pupil being larger). Initially the pupil is dilated and reacts slowly to light and near stimulus but over time it may become small and miosed. The condition is associated with reduced deep tendon reflexes and is confirmed by observing pupillary super sensitivity by constriction with diluted 0.125% pilocarpine drops.

Horner Syndrome

Horner syndrome or oculosympathetic palsy is an affliction of sympathetic nervous system presenting as unilateral ptosis, miosis of pupil, pseudoenophthalmos (due to lower eyelid ptosis), anhidrosis and (in congenital cases) with hypochromic heterochromia iridis (reduced iris pigment of affected eye) **(Fig. 13)**. About half of Horner syndrome in childhood are congenital with majority having history of forceps delivery or vacuum extraction with shoulder dystocia or fetal rotation. They may often have concomitant brachial plexus injury. Acquired causes include tumors such as neuroblastoma, rhabdomyosarcoma and trauma. Pharmacological testing though described is difficult to perform in view of difficulty in obtaining the agents such as cocaine and amphetamine.

MORE ON THIS TOPIC

Atkins E, Biousse V, Newman N. Optic neuritis and multiple sclerosis. In: Lorenz B, Barruat FX. Pediatric Ophthalmology, Neuro-ophthalmology and Genetics. Heidelberg: Springer; 2008.

Kanski J. Neuro-ophthalmology. In: Kanski J. Clinical Ophthalmology: a systematic approach. Philadelphia: Elsevier; 2007. pp. 785-836.

Simon J, Aaby A, Drack A, et al. Optic disc anomalies: basic and clinical course. San Francisco: American Academy of Ophthalmology; 2010. pp. 359-69.

Votruba M. Inherited optic neuropathies. In: Lorenz B, Barruat FX. Pediatric Ophthalmology, Neuro-ophthalmology and Genetics. Heidelberg: Springer; 2008. pp. 51-65.

Wilhelm H, Wilhelm B. Diagnosis of pupillary disorders. In: Schiefer U, Wilhelm H, William H. Clinical neuro-ophthalmology: a practical guide. Heidelberg: Springer Inc.; 2007. pp. 55-71.

Chapter 47.9
Strabismus and Motility Disorders
AK Amitava, Shivani Grover

Strabismus or squint implies a misalignment of the visual axes. Normal alignment of the visual axes of the two eyes is one where they meet at the object of interest: parallel if at infinity, and one of convergence if at near. If the misalignment is similar in all directions of gaze, it is termed as concomitant (nonparalytic); if it varies, then it is called inconcomitant (paralytic). Paralytic, as the name implies, is often subsequent to ocular muscle palsy subsequent to III, IV or VI cranial nerve palsy. At birth, about 67% newborns have exodeviation and 3% have esodeviation. Most esodeviations straighten out by 2 months and exodeviations by 6–8 months. *Any persisting deviation beyond these time limits warrants an ophthalmological consult.*

ETIOPATHOGENESIS

Concomitant strabismus occurs because of faulty innervational control from presumed supranuclear convergence and divergence centers and their connections to medial longitudinal fasciculus. Anatomical variations such as abnormal insertions of recti check ligament or associated fascia may play a role. It may be inherited as dominant trait. In *infantile esotropia*, the deviation is concomitant and unrelated to accommodative effort. On the other hand excessive convergence to accommodative effort causes variable esotropia, due to two pathophysiological mechanisms acting singly or in unison. These are: (1) excessive hyperopia, demanding an equally strong accommodative effort to clarify the image, which results in esotropia; and (2) a high accommodative convergence/accommodation (AC/A) ratio accompanied by mild to moderate hyperopia. *The tendency to exodeviation is natural, which is evident from the fact that the eyes acquire an outward position in sleep and under anesthesia (position of rest).*

RELEVANCE OF STRABISMUS IN CHILDREN

Why should a pediatrician be concerned about strabismus, especially its early presentation? This arises from the simple concept that the brain shuts off the form-visual input from the deviated eye, (possibly on account of inhibitory miss-matching input from the good eye) which then leads to *amblyopia,* a functional visual deficit. This is potentially reversible during the critical period thought of till approximately 7–10 years of age; a time-line eminently in the pediatricians' domain; especially since childhood strabismus is often neglected with an erroneous feeling, in both the community and care-givers that the *eye will straighten itself out over time.* Adverse psychological peer pressure during the sensitive growing years further compounds the problem. Strabismus often heralds an inner pathology, like optic atrophy causing sensory deficit strabismus; various intracranial infections, parasitic infestations and tumors/hydrocephalus often present with a paralytic strabismus.

Common terminology related to strabismus is defined in **Box 1**.

BOX 1 Common terminology related to strabismus

Visual axis: Line of sight, extending from fovea to object of regard.

Pupillary axis: Line passing through pupil center, anterior to posterior, which is usually *not* aligned with visual axis.

Angle kappa: Angle formed between visual and pupillary axes. The fovea is somewhat temporal in location compared to anatomically posterior most point of eye. This demands that the patient *rotate* the (posteriorly located) fovea *inwards* to ensure that image of an object directly in front of eye falls on fovea, which would obviously make the cornea go *outwards* (**Fig. 1**). The corneal light reflex thus bounces off somewhat nasal to the center of the pupil. It is this appearance which is termed a *positive (or nasal) angle kappa.* Normally the corneal light reflex is about 2–4 degrees nasal to the center of the cornea/pupil. If the fovea is located nasal to the pupillary axis, the posterior segment (with fovea) would rotate outwards to align with object of regard; resulting in a negative angle kappa, and corneal light reflex bouncing off somewhat temporal to the pupillary (or corneal) center giving false appearance of an inward deviation.

Orthophoria: Straight, well aligned eyes, without any tendency of either eye to deviate. This is not the norm, *a small phoria being usual.*

Heterophoria: Latent deviation of the eyes held in check due to binocular fusion. This can be eso- (= inward; nose-ward), exo- (= outwards; ear-ward), hyper- (= upwards) and hypo- (= downwards) phoria; with these listed terms prefixed. A phoria may manifest at times of stress, fever, concurrent illness, exhaustion, psychosocial stress, strong sunlight; causing intermittent strabismus.

Heterotropia: Manifest deviation of the eyes, not controlled by binocular vision. Depending on the direction it could be, eso-, exo-, hyper-, or hypotropia.

Conjugate movements or versions: Binocular movements in the same direction. There are the six cardinal directions of gaze to identify weak or overacting extraocular muscles; and the best way to obtain a photographic record of strabismus involves clicking pictures of eye in the nine directions of gaze (**Fig. 2**).

Disjunctive movements or vergences: Refers to movement of the two eyes in opposite directions which include convergence; the eyes turning inward and divergence; turning outward.

Ductions: Monocular rotations, which ignores position of other eye. These can be adduction; inward rotation, abduction; outward, supraduction (elevation); upward and infraduction (depression); downward rotation.

Primary deviation: Deviation of the paretic eye measured with the *normal eye fixing. Secondary deviation:* Deviation of the normal eye, measured with the *paretic eye fixing.*

In inconcomitant strabismus (paralytic/restrictive) secondary deviation is more than the primary.

Cover test: Small deviations are best detected by the *cover test,* which includes, covering each eye in turn while the patient is asked to (preferably) read/describe a target, *and observing the uncovered eye.* If in a case of strabismus, if the habitually fixating eye happens to be the one covered, *then the nonfixating eye will shift to take up fixation.*

Cover-uncover test (CUT): At times tendency to deviation is kept in check (and thus hidden/latent) by binocular fusional mechanisms. This may be made manifest by stressing the patient by breaking his fusion: either by covering one eye for some time (the CUT), or even better, by alternately covering each eye a number of times (the alternate cover test [ACT]). It is important to allow 3–4 seconds of cover (to effectively break fusion), and rapidly shift between the eyes (so that the child is not permitted to regain binocularity), to suspend fusion.

Pseudostrabismus: It is important to differentiate a true strabismus from a false impression of a strabismus (**Table 1 and Fig. 3**).

STRABISMUS ASSESSMENT

1. *Compensatory head posture (CHP)* This is adopted to avoid diplopia in recent onset (usually paralytic) strabismus in a visually mature system. The head tilt does what the extraocular muscle fails to accomplish: thus in a left lateral rectus (LR)

palsy, the head turns left, permitting fusion and binocular single vision in right-gaze; in the case of the right superior oblique (SO) palsy (an intorter) the head tilts to the opposite shoulder (left).

2. Ascertaining ocular positions in different directions of gaze.
   • Testing ocular motility binocularly (versions) and *then* uniocularly (ductions) with a torch in 9 gazes.
   • *Bruckner/Red reflex test* **(Figs 4 to 6)**: Observation of the red-glows simultaneously from the two eyes from a working distance with the larger spot light of the direct ophthalmoscopy. It gives information on:
     - Presence of strabismus → brighter reflex from deviated eye.
     - Gross refractive errors, and therefore anisometropia: Bigger crescents with more ametropia → superior crescents in hyperopia, inferior in myopia.

Figure 1 Left eye shows how the light reflex on the cornea (Hirschberg test) bounces off eccentrically, *despite* the fact that the fovea is in alignment with the object of regard, giving rise to angle Kappa

Table 1 Causes of pseudostrabismus

• Abnormal angle kappa
  – Too positive → pseudoexotropia
  – Negative → pseudoesotropia

• Wide bridge of the nose as in infants → Pseudoesotropia
• Prominent epicanthal folds → Pseudoesotropia
• Narrow interpupillary distance (due to horizontal globe displacements)
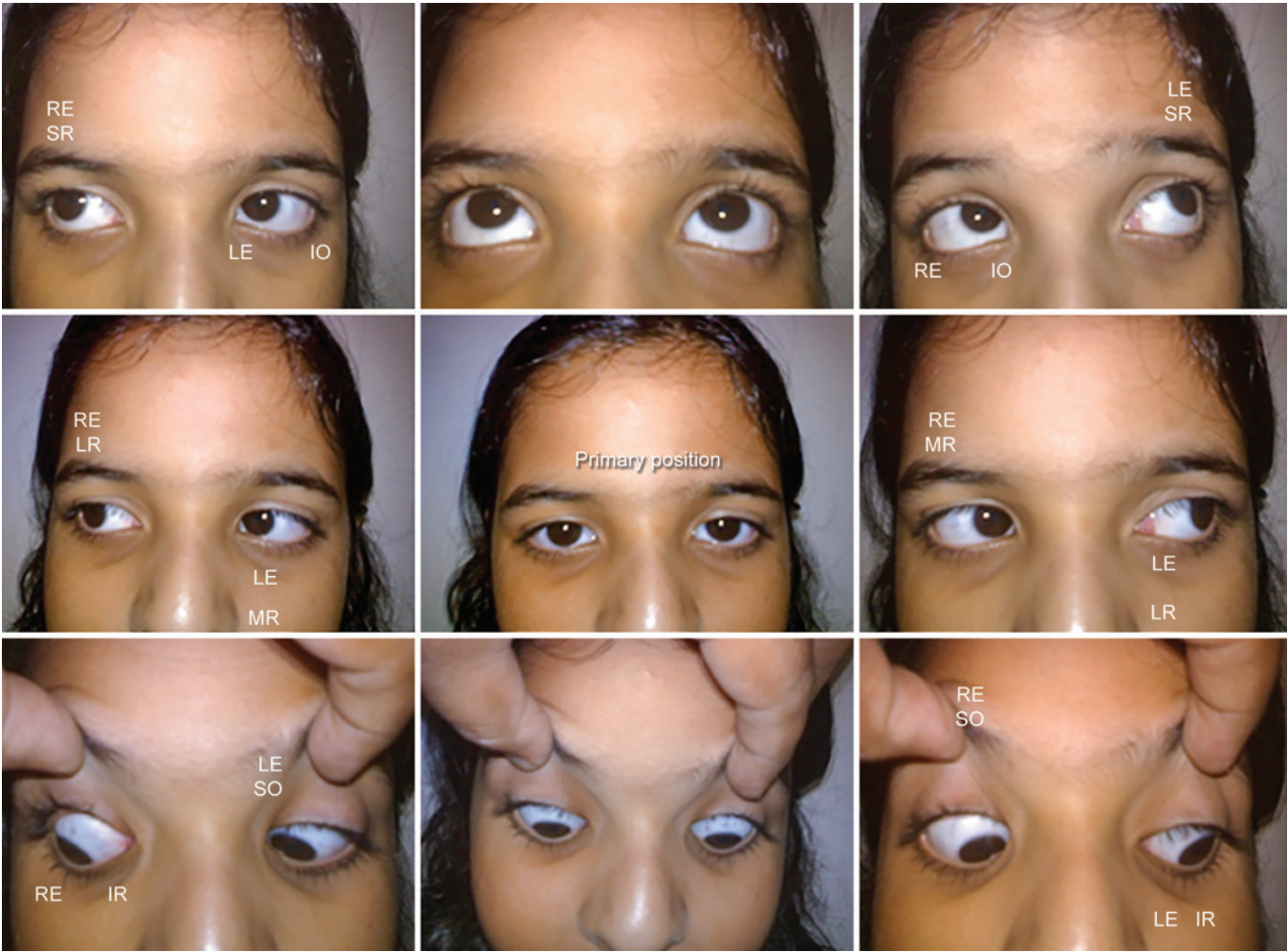
Figure 2 Six cardinal directions of gaze are labeled to show the yoke muscles, the actions of which are demonstrated
Abbreviations: SO, superior oblique; IO, inferior oblique; LR, lateral rectus; MR, medial rectus; IR, inferior rectus; SR, superior rectus; LE, left eye; RE, right eye.

Figure 3 This child has a pseudoesotropia on account of the broad nasal bridge (note the central corneal reflections)

| Myopia 2–3 D | Myopia 1 D | Emmetropia | Hyperopia +1 D | Hyperopia +2–3 D |

Figure 4 *Bruckner reflex:* Aid to reflexes and shadows/crescents in refractive errors (the lighter color represents the brighter reflex)

Figure 5 *Bruckner test:* Note the bright reflex from the deviated left eye, suggestive of strabismus
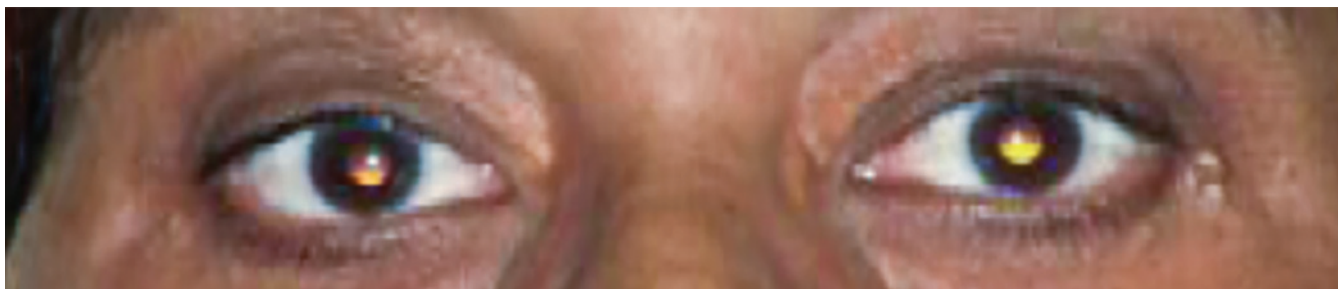
Figure 6 *Bruckner test:* Showing anisometropia. The inferior crescent in both eyes suggests a myopic error, note that the crescent is brighter and larger in the left eye as compared to the right suggesting a higher myopic error in the left eye

- Media opacities → block/diminish the reflex as in cataracts, retinoblastoma, and vitreous hemorrhage.
- Pupillary reactions, including relative afferent pupillary defect (RAPD), by swinging the ophthalmoscope beam from one eye to the other, when pupil contractions are picked up as contracting orange discs.
- After dilatation, festooned pupil or broken synechiae may be evident.
- One can reach out from a working distance and cover each eye in turn, to do the cover-test to pick up tropias.

3. Hirschberg corneal reflex **(Fig. 7)**.

Esotropia (Table 2)

Infantile Esotropia (Fig. 8 and Table 3)

The most common strabismus in infancy, it is seen in less than1% neonates and resolves by 2 months. Pathological esotropia occurs prior to 6 months of age, has a large angle, constant esotropia, with emmetropia or low hyperopia (≤ +2D). Motor defects like over action of the inferior oblique (IO), latent nystagmus and dissociated vertical deviation **(Figs 9A and B)** are seen in 50–70% cases **(Table 3)**.

Management Bimedial rectus recession under general anesthesia is the preferred surgery for infantile esotropia. In dense amblyopia uniocular recession of medial rectus combined with lateral rectus resection of one eye may be considered.
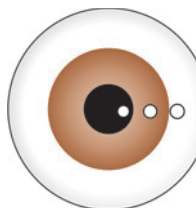
Tested from a working distance with a penlight, with examiner standing behind torch in front of eye being tested. If reflection/reflex bounces off pupillary edge, it is considered about 15° deviated, mid-peripheral iris 30°, limbus 45°, beyond limbus 70°.

Figure 7 Hirschberg corneal reflex (HBCR) fundamentals

Table 2 Classification of esotropia

• Infantile esotropia (common)

• Acquired esotropia
 – Refractive esotropia (common)
  - *Hypermetropic esotropia:* Similar deviation for distance and near, correctable with plus lenses
  - *Accommodative esotropia:* Esotropia alone or more (by ≥ 10 prism diopter [pd]) at near—often need additional plus at near in the form of bifocals
  - *Partially refractive esotropia:* Some residual esotropia remains despite full cycloplegic correction

• Acquired non-refractive ET (uncommon)

Figure 8 Infantile alternating esotropia; note the temporally decentered corneal reflex. It is interesting to note that the broad nasal bridge exaggerates the esotropic appearance

Figures 9A and B Dissociated vertical deviation (DVD) right eye more than left eye. This does not follow Hering law
(*Source:* Dr Bilu Balan P).
(A) The right eye floats up (and extorts) behind translucent occluder. With cover shifted to left eye, right floats down, without a concomitant hypotropia in left eye, as might be expected with a right hypertropia. Instead left eye makes a similar movement upwards, although of a lesser amount;
(B) Other tests for dissociated vertical deviation (DVD):
   • *Red filter test:* When placed on either eye, red image is always inferior.
   • *Bielschowsky phenomenon:* Increasing density filter over fixing eye causes floating eye to come down.
   • Measured by *Prism under cover test.*
   If warranted, surgery consists of large recessions of superior rectus.

Table 3 Clinical features of infantile esotropia. Variable presentation, all may not occur

• *Constant large angle esotropia (and therefore central scotomas):* Usually ≥ 30 pd, more likely ≥ 40 pd, often 40–70 pd
• Onset prior to 6 months of age
• Insignificant refractive error (not >+ 2D in children ≤ 1 year age, and <+3D in older children). When in doubt a trial of lenses will establish that the glasses have no effect on the strabismus angle
• May *cross-fixate:* Seeing left side of field with the right crossed eye, and right side of field with the left cross eyed. Such cases may thus not (or be reluctant to) abduct the eyes, and instead adopt a *head turn* to keep one eye looking ahead. Momentary patching one eye for an hour will allow complete abductions to be demonstrated
• *Amblyopia* is common*:* It should be strongly suspected and antiamblyopia therapy undertaken, especially when there is a constant esotropia with little or no cross fixation
• Long standing cases may show limited forced abductions, due to tight medial rectus, which may show up as horizontal incomitance
• Other associations which may occur are a *dissociated vertical deviation, latent nystagmus, face turn, oblique dysfunction, and A or V phenomenon*

Accommodative Esotropia

Common in toddler age (increased reading demand and developing accommodation), the entity is subsequent to excessive hyperopia. The squint is variable, proportionate to accommodative desire **(Fig. 10)**. This strabismus is fully correctable with spectacle prescription of full cycloplegic correction. For those with high AC/A ratio, esodeviation at near is greater, and requires use of plus bifocals along with distance hyperopic correction **(Table 4)**. **Flow chart 1** shows an approach to a child with esotropia.

Exotropia

Intermittent Exotropia

Common, with exophoria breaking down during periods of in-attentiveness into a manifest exotropia **(Figs 11A and B)**. These patients demonstrate excellent fusion and stereopsis during their straight eyed phases and show large hemiretinal suppression during tropic phase **(Fig. 11)**. It begins in toddler age of 2–4 years, shows a progressive worsening in frequency and duration of manifest deviation, till a constant alternating exotropia (XT) occurs **(Figs 12A and B)**. Photoaversion leading to squinting of one eye is considered pathognomonic **(Fig. 13)**. Meticulous history, documenting deterioration should suggest timely surgical intervention **(Table 5)**.

Management Uniocular recession-resection procedure—weakening the lateral rectus and strengthening the medial rectus.

Inconcomitant/Paralytic Strabismus

The differentiating features are given in **Table 6**. Congenital onset paralytic strabismus may not show these features since the sensory system is still *malleable* and adapts rapidly. Paralytic strabismus heralds a serious neurological lesion, warranting a neuroradiological evaluation.

Sixth Nerve (Lateral Rectus) Palsy

It results in an esodeviated eye on account of unopposed action of the medial rectus; it causes horizontal uncrossed diplopia **(Figs 14A to C)**. It is often a *false localizing sign* in cases of raised intracranial pressure. A unilateral transient VI and VII nerve palsy may happen after a febrile illness or immunization.

Treatment A time period of 6 months for spontaneous recovery is given. In the interim, botulinum injection into the antagonist medial rectus to allow better fusion in the straight ahead position can be tried. After the waiting period, residual palsy is tackled by surgery involving shifting the vertical recti, fully or partially to the insertion of the paralyzed lateral rectus.

Fourth Nerve Palsy

Such children present with difficulty in going downstairs, or eating food or reading, since the superior oblique (intorting muscle) is employed for down gaze. The child presents with a head tilt to the opposite side, with a noticeably higher eye, which rises further on force-tilting to the same side (Bielschowsky test) **(Fig. 15)**. Often congenital, it arises due to an abnormal tendon, and is associated with ipsilateral smaller face. On account of its dorsal exit from the brainstem, and long intracranial course, this nerve is most susceptible to trauma.

Treatment Traumatic cases often resolve spontaneously, and should be observed for 6–12 months. Surgery involves weakening ipsilateral inferior oblique (antagonist of SO) or contralateral inferior rectus (yoke of SO) or tucking of lax SO tendon.
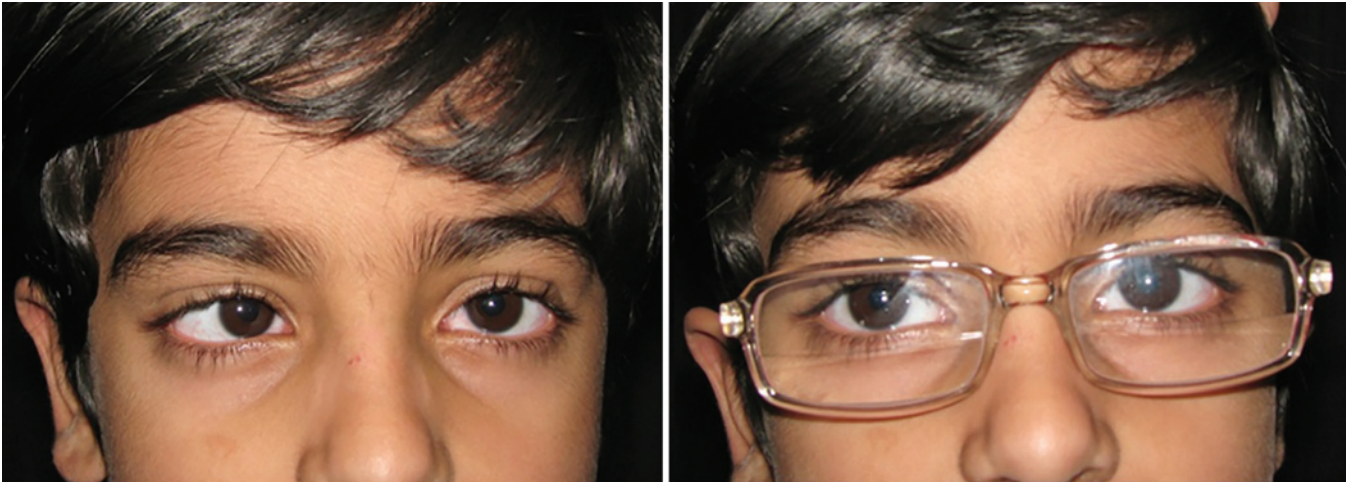
Figure 10 Refractive esotropia corrected with glasses: Note the bifocal segment for the high accommodative convergence/accommodation (AC/A) ratio

Table 4 Types of refractive esotropia and suggested line of therapy

Refractive esotropia: High hyperopia, usually > + 4D	Full cycloplegic correction
High AC/A ratio: These case are either straight at distance with esotropia only at near, or a significant greater (i.e., by > 10 pd) esotropia at near.	Will need either correction at near or a bifocal add for near. Give bifocals only if: the child is seeing through them *and* it is resulting in a residual esotropia of < 10 pd (this usually allows some binocularity). Usually *flat topped or executive bifocals* are prescribed
Partial refractive esotropia: Only part of the angle is corrected by addressing their hyperopia or high AC/A ratio	Correct refractive error as earlier. Surgery is indicated for the residual esotropia

Abbreviation: AC/A ratio, accommodative convergence/accommodation ratio

Flow chart 1 Algorithm showing approach to a child presenting with esotropia

Esotropia

Do a Bruckner test:

- **Symmetrical**
  - Central Hirschberg corneal reflex
  - No movement on alternate cover test

    Pseudoesotropia
    Look for broad nasal bridge, epicanthal folds, craniofacial dystrophies, narrow interpupillary distance and abnormal angle kappa

- **Asymmetrical**
  - Brighter or lighter reflex suggests strabismus, supported by:
    - Temporal Hirschberg corneal reflex
    - Outward movement on alternate **cover test**

  Check for ocular movements (Versions and ductions)

  - Significant abduction deficits

    Look for any significant change in the width of palpebral aperture

    - Yes → Probably **esotropic Duane's**
    - No → Probably **6th nerve palsy**

  - Ocular movements complete in all directions of gaze

    Use strong plus lens in front of the fixating eye and see whether eyes straightens out

    - Yes → **Refractive esotropia**
    - No → **Infantile esotropia**

Figures 11A and B Intermittent exotropia. (A) During the manifest phase of tropia: Notice the right eye is exodeviated; (B) During the nontropic phase: By utilizing his fusional convergence the boy has aligned his eyes
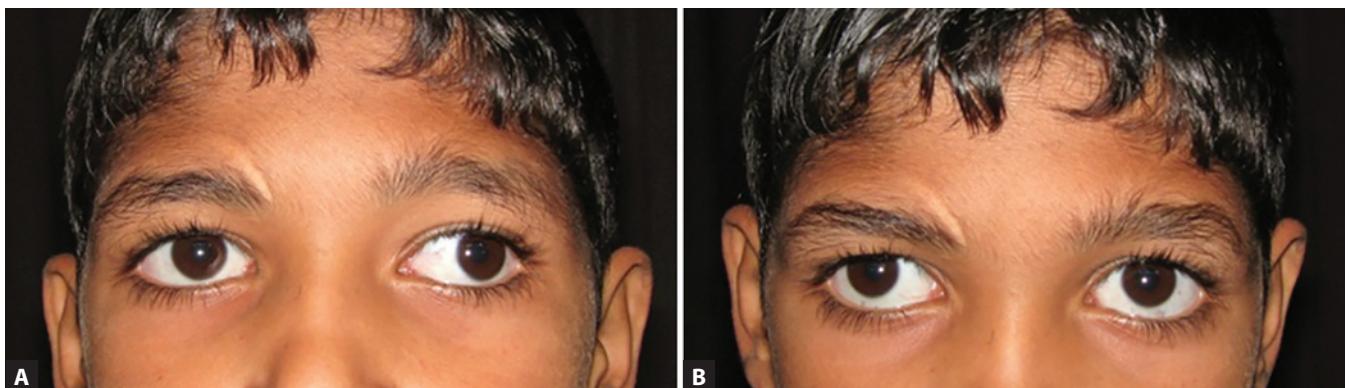
Figures 12A and B Alternate exotropia. Notice the Hirschberg reflex—(A) Left eye is exotropic; (B) Right eye is exotropic

Third Nerve Palsy

Congenital is more common than acquired with the latter seen in head trauma, infections, tumor, aneurysm, meningitis, or post-viral syndrome **(Fig. 16)**. Complete third nerve palsy presents with ptosis (weakness of levator palpebrae superioris), fixed dilated pupil (ciliary muscles), down and out eye position (action of SO, LR**)**. Congenital cases are usually incomplete, unilateral and

Figure 13 Child with intermittent exotropia squinting in sunlight *photo aversion*. The child has a tendency to narrow palpebral aperture of right eye, which is also the eye manifesting exotropia. Interestingly exotropia is more common closer to the equator

Table 5 Signs of progression of intermittent exotropia

• Increasing frequency and duration of manifest phase of intermittent exotropia
• Development of secondary convergence insufficiency
• Increase in size of basic deviation
• Suppression, as evidenced by lack of diplopia in manifest phase
• Decrease or loss of stereoacuity

Table 6 Paralytic versus nonparalytic strabismus

	Paralytic	*Nonparalytic*
Age of onset	Any age	Usually congenital or during childhood
Type of onset	Often sudden	Rarely sudden
Deviation	Secondary > primary	Secondary equals to primary
Diplopia	Common	Uncommon
Systemic/neurological associations	Present	Absent

associated with abnormal synkinesis and miosis and warrant a thorough neurological work-up.

Treatment Underlying disease is treated; surgery is planned only after ruling out spontaneous recovery which may take 6–12 months. Surgery is complicated since most muscles are affected.

SPECIAL FORMS OF STRABISMUS

Duane Retraction Syndrome

Absent innervations by abducens nerve and abnormal innervations by the oculomotor nerve to LR causes cocontraction of both the horizontal recti, causing globe retraction, along with narrowing of the palpebral aperture, and restriction to abduction/adduction **(Fig. 17)**. Up shoots/down shoots of the eyes are also common. Associated neurologic deficits involving brainstem like crocodile tears, sensorineural hearing loss or ocular dermoids, ear dysplasias, accessory ear tags (Goldenhar syndrome), skeletal defects and oculocervicorenal syndrome (Klippel-Feil anomaly) are common.

Treatment

Therapy is often unsatisfactory. The child (and parents) are counseled that head posture is allowing fusion and binocular single vision. Teachers should allow the child to sit to side of the class to which the head is turned. Surgery is complicated and only undertaken in marked head turn or severe palpebral aperture changes. Associated refractive error or amblyopia has to be addressed.

Brown Superior Oblique Tendon Sheath Syndrome (Fig. 18 and Table 7)

This occurs due to a tight SO tendon or its sheath. Since, the superior oblique is the antagonist of the IO muscle, and must relax during contraction of IO, features are essentially of IO palsy: which is a failure to elevate the eye primarily in adduction. If the *elevated eye* is moved from abducted to adducted position, it shows a down drift with widening of the palpebral fissure. Surgery requires the release of the mechanical limitation, since the cause varies, so does the management.

Monocular Elevation Deficiency (Double Elevator Palsy) (Fig. 19)

Usually uniocular, the child is unable to elevate the eye past the midpoint, and may be hypotropic. Three explanations exist: firstly the inferior rectus (IR) may be scarred/contractured, (blow out fracture of the orbit) preventing elevation (SR, IO). In this case Bells phenomenon and forcible elevation under anesthesia is absent. Secondly, the superior rectus (SR) may be palsied: bells absent but forcible elevation possible. Congenital cases are often accompanied by a developmental ptosis, or jaw-winking synkinesis. Thirdly, monocular elevation deficiency (MED) may occur with normal Bells and free forced supraductions: when it suggests a supranuclear etiology in presumed center(s) of gaze-elevation.

Figures 14A to C Post-traumatic sixth nerve palsy of right eye—(A) Note abduction deficit of right eye in right gaze; (B) The eye is esodeviated in primary gaze and head is turned to right to compensate for abduction deficit; (C) Normal movement in left gaze
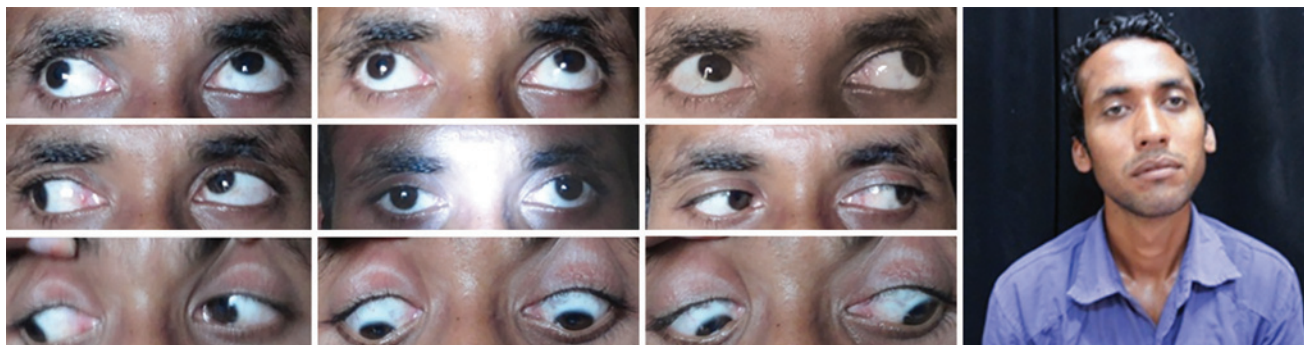
Figure 15 Fourth nerve palsy of left eye; note that left eye is hypertropic in primary position, with limitation of movement in dextrodepression, upshoot in dextroversion, more obvious in dextroelevation. Also note head tilt to opposite side
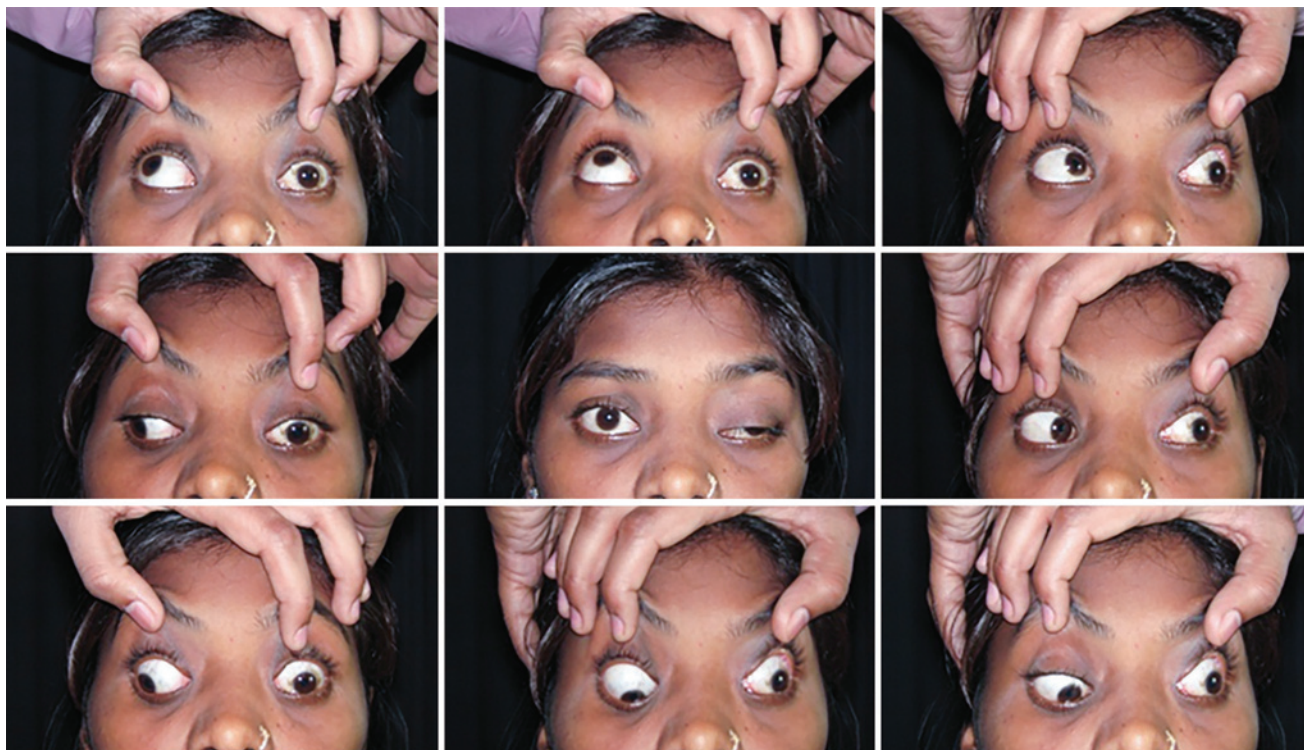
Figure 16 Third nerve paralysis of left eye; observe ptosis, and limited elevation and adduction

Figure 17 Duane retraction syndrome left eye: note limited abduction of left eye in left gaze along with widening of palpebral aperture. In right gaze, there is limited adduction of left eye, with narrowing of palpebral aperture on account of the cocontration of horizontal recti

Möbius Syndrome

This congenital condition presents with facial weakness, and either abduction deficit (often bilateral) or horizontal gaze palsy (HGP), along with limb malformations, cranial dysmorphism and laryngeal/pharyngeal dysfunction. Affected children may suckle poorly and have mask like facies with an open mouth (VII nerve palsy), and straight/uniocular esotropia (bilateral or unilateral VI nerve palsy). Other defects include deafness, webbed or

Figure 18 Brown syndrome: Note limitation of elevation of right eye, most apparent on adduction

Figure 19 Monocular elevation deficiency: Note elevation deficit of left eye in both adduction and abduction

Table 7 Brown syndrome: Clinical features

• In adduction:
– Deficient elevation
– Down shoot
– Widening of palpebral fissure
• Elevation deficiency less in midline and least (or nil) in abduction
• Divergence in up gaze causing a V-pattern
• Positive forced duction test for superior oblique
• May have primary hypotropia
• Anomalous head posture

Table 8 Ophthalmology options in strabismus and rationale

Refractive correction	Improves vision, aids in fixation
Prisms	May be useful in patients whose nystagmus dampens in convergence (convergence dampening nystagmus) or gaze to one side (null point nystagmus)
Extraocular muscle surgery	• By *shifting the null*: Appropriately recessing (weakening) the *pulling* muscles alone (called the Andersons procedure) or combining it with resection (strengthening: Kestenbaums part) • By weakening all the horizontal muscles to decrease the velocity and increase foveation time • By *disconnection/reconnection* surgery, involving tenotomy of the horizontal muscles with reattachment at their original insertion
Botulinum toxin	Injected retrobulbar 25 IU, in acquired nystagmus to reduce oscillopsia

supernumerary digits, muscle defects of chest, neck and tongue and rarely absence of hands and feet. Speech and swallowing defects commonly occur. Neuroimaging studies throw up heterogeneous findings: from nil to intracranial calcifications, brainstem hypoplasia or ischemia. It is felt that Möbius syndrome results due to a variety of insults such as ischemia or prenatal drugs such as misoprostol (a synthetic prostaglandin) or a benzodiazepine.

NYSTAGMUS

This is repetitive, to and fro, involuntary eye movements initiated by slow drifts. The corrective response could be a fast saccade (jerk nystagmus) or again a slow drift (pendular nystagmus). This helps to differentiate it from nystagmoid movements; in which a saccade intrudes and takes eyes off the target.

What keeps the eyes in position? Three mechanisms working together: fixation (which needs a good vision and normal motor mechanism), vestibulo-ocular reflex and the neural integrator. The last essentially consists of structures within the brainstem and cerebellar complex.

Physiological Nystagmus

It is of three types: (1) rail-road nystagmus also called optokinetic nystagmus (OKN); (2) end point nystagmus (on account of holding gaze in such an eccentric point that it stresses neural integrator);

and (3) vestibular nystagmus, elicited by chair rotation in darkness, or with minimal inconvenience by minimal ice water caloric test (provided ear drums are intact). The importance of work-up of *pathologic nystagmus* lies in (1) the possibility of benefit with treatment (see **Table 8**); and (2) knowing specific patterns to help in neuroanatomical localization **(Table 9)**.

Ideally nystagmus should be described in terms of *direction* of jerk: horizontal, vertical, torsional or mixed; whether jerk or pendular; congenital or acquired. While examining, asynchrony is checked. Compare the two eyes; they may differ in size of oscillation (dissociated) or in direction (disconjugate). What happens on covering one eye? This may uncover a latent nystagmus, with fast phase beating towards the fixating eye, often seen with infantile/congenital esotropia. Does it dampen with near fixation? Is there a compensatory head turn? This suggests a *null point* where nystagmus is dampened in lateral gaze, with a compensatory head turn to bring the *null point* straight ahead. Peripheral vestibular nystagmus is often kept in check with fixation: this thus becomes apparent on abolishing fixation. This is best carried out while doing direct ophthalmoscopy of one eye, and covering the other eye to

Table 9 Some neurologically important nystagmus

Nystagmus type	Characteristic features	Remarks/Neuroanatomic localization
A: When eyes are close to central position		
1. Peripheral vestibular nystagmus	Mixed jerk; suppresses with fixation; beats away from lesion; increases when eye turn towards quick phase (Alexander's law)	Accompanied by vertigo
2. Congenital nystagmus	Largely horizontal; accentuated by fixation (attention, anxiety); characteristically shows *optokinetic inversion*	May be pendular or jerk; sometimes has compensatory head posture
3. Latent/manifest latent nystagmus	Evident on covering one eye; jerks towards fixating eye	May manifest when patient *chooses to fixate with one eye*; often with infantile esotropia
The above 3, usually need no further neurological evaluation. Both downbeat and upbeat nystagmus are attributable to a central involvement of the vestibular pathway (in contrast to 1 above)		
4. Periodic alternating nystagmus	Horizontal reversing about every 2 minutes	Midline cerebellum (nodulus and uvula)
5. Downbeat nystagmus	Best evoked on looking downward and laterally	Lesions in vestibule-cerebellum, craniocervical anomalies, such as Arnold-Chiari malformation; drugs
6. Upbeat nystagmus	Evoked on looking up	Less well localized; medulla or superior cerebral peduncle
7. Acquired pendular nystagmus	Usually varying directions: oblique, elliptical or circular; often asynchronous	Disorders of central myelin as may occur in multiple sclerosis or brainstem stroke
8. See-saw nystagmus	One eye rises and intorts, other falls and extorts, followed by reversal	Pituitary lesions/near chiasmal syndromes
B: Nystagmus occurs on moving eyes to an eccentric position		
9. Gaze evoked nystagmus	Quick phases away from central position	Common; lesions of cerebellum and brainstem impairing the neural integrator. Different from the physiological end point nystagmus. *Drugs:* Sedatives, anticonvulsants, intoxicants
10. Abducting nystagmus	Dissociative; nystagmus greater in abducting eye	Lesion in medial longitudinal fasciculus, part of internuclear ophthalmoplegia (INO)
11. Bruns nystagmus	Low frequency, large amplitude on looking ipsilaterally (defective gaze holding); high frequency, small amplitude looking contralaterally (vestibular imbalance)	Tumors in the cerebellopontine angle
12. Convergence-retraction nystagmus	Induced by upgaze; aided by down-rotating OKN stripes; eyes retract with convergent jerks	Dorsal midbrain; periaqueductal syndrome of parinaud, pinealoma

Abbreviation: OKN, optokinetic nystagmus

remove fixation, and observing the effect on retinal motion in the eye being viewed.

A Practical Approach to a Child with Nystagmus

Although detailed evaluation of wave forms, using electronystagmography, videography and other electro-physiological testing is ideal, a lot can be gleaned from careful observation.

- A careful look with a torch at the *anterior segment* can identify obvious causes like developmental corneal opacities or cataracts.
- This can be followed-up by a direct *ophthalmoscopy* under dilation: apart from confirming the earlier findings, this may in addition help pick up fine nystagmus, by magnifying the movement (Keep in mind that since one is seeing the posterior movements, directions appear reversed as compared to corneal movement). More importantly, it should help identify visible posterior segment pathology: optic atrophy, heredomacular dystrophy, cherry-red spot for instance. Remember some ocular visual deficit causes cannot be *seen* on retinal visual examination, and may need electroretinography/electro-oculography tests, e.g., cone dystrophy, Lebers

amaurosis, achromatopsia. In most macular pathology, photophobia is characteristic.

- Three other points can be quickly dispensed with:
  - Is there any craniofacial dysostosis or osteoporosis?
  - Is there a growth disorder or features of hypothyroidism?: suggesting a pituitary pathology (suprasellar tumors) and
  - Any drugs implicated? Rule out sedatives, antiepileptics, fetal alcohol syndrome: these affect the neural integrator adversely.
- Other associated *CNS symptoms* often help elucidate the picture:
  - Tachypnea should draw attention to Joubert syndrome: problem lies in cerebellar vermis and brainstem (*molar tooth sign* on magnetic resonance imaging [MRI]). Other features may include ataxia, sleep apnea and hypotonia.
  - Association of ataxia and/or dystonia might indicate Pelizaeus-Merzbacher disease (a leukodystrophy; with sex linked inheritance) or dystonic cerebral palsy.
  - Presence of lactic acidosis may point towards acid aminopathies, organic acidemias and Leigh disease
  - Is there cerebellar ataxia?
  - Seizures should suggest perinatal hypoxia, Batten disease, neurolipidosis or subacute sclerosing panencephalitis.

– With neuropathy one should rule out giant axonal neuropathy and metachromatic leukodystrophy.
– Developmental delay may hint at peroxisomal disorders or hypothyroidism.
– Dysmorphism with skull malformation may provide a clue to structural brain defects.

Nystagmoid Movements

These are inappropriate saccades, which take the eye away from fixation. *Square wave jerks*, are small, conjugate saccades; with eyes returning to fixation; often in progressive supranuclear palsy. *Macrosaccades* are a burst of larger saccades which wax and wane, and take eyes on either side of fixation; and suggest a midline cerebellar disease or pontine lesions. *Saccadic pulses* are brief intrusions, with eyes rapidly drifting back; often noticed in internuclear ophthalmoplegia. If there are no intervals between pulses, they are termed *ocular flutter* (when horizontal) or *Opsoclonus* (chaotic, with a mix of horizontal, vertical and rotatory saccades): these occur in parainfectious brain stem encephalitis, paraneoplastic syndromes, metabolic-toxic states or idiopathic.

MORE ON THIS TOPIC

A classification of eye movement abnormalities and strabismus (CEMAS). From: www.nei.nih.gov/news/statements/cemas.pdf. Accessed December 09, 2014.

Enhanced Bruckner test. Alaska Blind Child Discovery. From: www.abcd-vision.org/vision-screening/bruckner.html. Accessed December 09, 2014.

Gunton KB. Advances in Amblyopia. In: What have we learned from PEDIG trials? Pediatrics. 2013;131:1-8.

Red Reflex Examination in Neonates. Infants and Children. From: http://pediatrics.aappublications.org/content/122/6/1401.full.html. Accessed December 09, 2014.

Taylor D, Hoyt CS. Pediatric ophthalmology and strabismus. 3rd edition. London: Saunders; 2005.

Wright KW. Pediatric ophthalmology and strabismus. 3rd edition. USA: OUP; 2012.

Chapter 47.10
Eyelid, Orbit and Lacrimal Sac
Apjit Kaur

GENETIC ANOMALIES

Eyelid Anomalies

Isolated congenital ptosis is usually not heritable. A few reports indicate the possibility of dominant inheritance and linkage to 1p34.1-p32. The *ZFH4* gene (8q21.1) may be a candidate gene. Autosomal dominant blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) results from mutation or deletion of the *FOXL2* gene. Congenital fibrosis of the extraocular muscles (CFEOM) types 1, 2 and 3 are caused by mutations in *KIF21A* (12q12), *PHOX2A* (11q13) and *TUBB3* (16q24.3) or *KIF21A* genes respectively. Congenital myasthenic syndromes are genetic disorders associated with mutations in different genes encoding proteins involved in presynaptic, synaptic or postsynaptic neuromuscular transmission, including the *RAPSN* gene (11p11.2-p11.1), and the muscle-specific protein kinase (*MUSK*, 9q31.3-q32) gene. Chronic progressive external ophthalmoplegia (CPEO) and Kearns-Sayre syndrome (KSS) are sporadic diseases. Autosomal recessive or dominant CPEO may be caused by nuclear DNA mutations in the *POLG* gene (15q25) or *ANT1* (4q34) and *C10orf2* (10q24) genes respectively. Oculopharyngeal muscular dystrophy (OPMD) is caused by expansion of a heterozygous trinucleotide repeat (CTG) in the *DMPK* gene (19q13). The neurofibromin protein, encoded by the *NF1* gene (17q11.2) is a tumor suppressor gene. Upper eyelid coloboma seen in oculoauriculovertebral spectrum (OAVS) may be inherited in an autosomal dominant manner, associated with multiple loci and one known gene, *SALL1* (16q12.1).

Genetic Anomalies of Orbit and Eyeball

Crouzon, Apert, Pfeiffer, Muenke and Saethre-Chotzen syndromes are autosomal dominant and occur due to mutations in the *FGFR2*, *FGFR2*, *FGFR1 FGFR3*, and *TWIST1* genes respectively. Anophthalmia and microphthalmia may occur in isolation or in association with systemic disease. Genetic causes include chromosomal aberrations (e.g., trisomy 13 and 18), mutations or deletions involving the *SOX2*, *SIX6*, *STRA6*, *HESX1*, *BCOR*, *SHH*, *PAX6* and *RAX* genes. Syndromes such as Goltz, Meckel-Gruber, Seckel, cerebro-oculo-nasal, branchio-oculo-facial, Walker Warburg and Fraser syndrome, can be caused by homozygous or compound heterozygous mutations in the *FRAS1* (4q21), *FREM2* (13q13), or *GRIP1* genes (12q14). The Manitoba oculo-trichoanal syndrome (MOTA) is also caused by mutations in *FRAS1*.

Genetics of Lacrimal System

Congenital alacrima, a rare autosomal dominant condition is caused by mutations in the gene encoding *FGF10* (5p12). Lacrimo-auriculo-dento-digital syndrome (LADD), also known as Levy-Hollister syndrome, is an allelic disorder with a more severe phenotype. Branchio-oculo-facial syndrome due to *TFAP2A* gene mutations, 6p24.3, trisomy 21 (Down syndrome), Johanson-Blizzard syndrome (*UBR1* gene mutations, 15q13-21.1), dyskeratosis congenita (*DKC1* gene mutations, Xq28) and the Treacher-Collins-Franceschetti syndrome are associated with nasolacrimal duct obstruction.

Figure 1 Bilateral epiblepharon

DISORDERS OF EYELIDS

Congenital Anomalies of Eyelids

Epiblepharon

It is a horizontal fold of skin, present over the lower eyelid in chubby babies and orientals **(Fig. 1)**. Spontaneous resolution occurs as facial fat reduces and facial growth occurs. Treatment by spindle excision of skin and orbicularis muscle layer is indicated in patients where resolution does not occur.

Epicanthus

Epicanthus is a bilateral, fetal, semilunar fold of skin extending between upper and lower eyelid that usually disappears at birth, except in Mongolian races. Depending upon the extent of the fold, it is referred to as epicanthus supraciliaris (eyebrow to lacrimal sac), epicanthus palpebralis (upper eyelid to inferior orbital margin), epicanthus tarsalis (upper eyelid tarsal region to medial canthus), and epicanthus inversus (from lower eyelid to medial canthus). This may occur in isolation or be associated with other abnormalities like ptosis, ankyloblepharon, telecanthus (Blepharophimosis syndrome). No treatment is needed. However, when treatment is indicated for cosmetic reasons, surgical correction using a V-Y procedure or Mustardes four flap technique is employed.

Telecanthus

At birth, normal inter medial canthal distance is 20 ± 2 mm and normal interpupillary distance is 39 ± 3 mm. At age 2 years, the former reaches 26 ± 1.5 mm and the latter reaches 48 ± 2 mm. Telecanthus refers to an increased intermedial canthal distance, with normal interpupillary distance. It may occur in isolation or as an association with epicanthus and blepharophimosis. Surgical correction is done using V-Y procedure and/or transnasal wiring.

Blepharophimosis

Narrowing of the palpebral aperture is referred to as blepharophimosis. When it occurs in association with ptosis, epicanthus, flattening of the supraorbital ridges, refractive errors, strabismus and nystagmus it is referred to as blepharophimosis syndrome (BEPS) **(Fig. 2)**. BEPS may be type 1 or 2, may be associated with infertility. The syndrome is inherited in an autosomal dominant pattern. Depending on the amount of eyelid deformity, patients undergo a staged repair of the eyelid defects.

Figure 2 Blepharophimosis syndrome

Figure 3 Bilateral euryblepharon

Recently, there is a recent shift towards planning single stage surgery for correction of the multiple defects.

Ankyloblepharon
Partial or complete fusion of the eyelid margins, leading to shortening of the palpebral aperture is referred to as ankyloblepharon. When the fusion of the two lids is by a single or multiple tags, it is referred to as ankyloblepharon filiformadnatum. Ectodermal defects, cleft lip/palate, hydrocephalus or meningomyelocele may be associated. Treatment is by splitting the union or tags.

Euryblepharon
It is a congenital generalized enlargement of palpebral aperture, lateral end more than medial. It causes lateral displacement of lateral canthus **(Fig. 3)**. The wider lateral canthus is associated with inferior displacement of lower eyelid (mimicking ectropion). Occurrence of euryblepharon may be isolated or inherited as an autosomal dominant trait. No treatment is advised.

Distichiasis
This is a sporadic or autosomal dominant trait, where an extra row of eyelashes is present on the lower eyelid. The upper eyelid is rarely involved and patient may be asymptomatic. Treatment involves removal of the extra row of eyelashes either surgically or by using electrocautery/cryotherapy. The latter leads to post-treatment pigmentary changes on eyelids.

Entropion
Congenital entropion is the inturning of lower eyelid margin, resulting in epiphora due to corneal irritation. Entropion associated with epicanthus or epiblepharon, results from a hypertrophic orbicularis oculi muscle and is often familial. Surgical correction by spindle excision of skin muscle complex is treatment of choice.

Ectropion
Congenital ectropion of the eyelid margin (outward turning) rarely occurs in isolation **(Fig. 4)**. The anterior lamellar shortening is part of the generalized tightening of the skin as in *Collodion* babies. Lubricants and emollients are used on the skin to result in softening of the stretched tissues. Sometimes grafting (to increase the anterior lamella) may be required in persistent cases.

Blepharoptosis
Congenital ptosis, results from a dystrophic levator palpebrae superioris muscle. It is the most common congenital eyelid anomaly, is usually unilateral and sporadic **(Fig. 5)**. Ptosis resulting

Figure 4 Bilateral ectropion in a *Collodion* baby

Figure 5 Unilateral congenital simple ptosis

from congenital third cranial nerve palsy or Horners syndrome is not conventionally referred to as congenital ptosis. Superior rectus muscle weakness and jaw winking phenomenon (due to aberrant innervation) **(Fig. 6)**, anisometropia and strabismus may be associated. Due to the dystrophic nature of the levator muscle, the affected eyelid is lower in position in primary gaze and higher

Figure 6 Congenital ptosis left upper eyelid with Jaw winking phenomenon

Figure 7 Stye right lower eyelid

in down gaze, than the contralateral normal eyelid. Compensatory chin elevation occurs in moderate/severe bilateral cases, frontalis muscle overaction compensates unilateral cases. Ptosis is graded as mild, moderate or severe depending on the amount of levator action and palpebral fissure height. Bells phenomenon (uprolling of eye ball on eyelid closure) and corneal sensation evaluation are important in surgical assessment. Indications for treatment of ptosis are cosmetic and visual. Treatment is surgical; procedure choice depends on ptosis severity.

Inflammations of Eyelids

Blepharitis

Inflammation of eyelid margins may be ulcerative or squamous, acute or chronic with the latter being commoner. *Staphylococcus aureus, Propionibacterium, Moraxella* species, Herpes simplex are the common offenders. Child presents with itchy red eyelids, burning sensation, eyestrain and watering. Seborrheic dermatitis of scalp may be associated. Treatment is instituted by combination of regular cleaning with isotonic solutions, hot fomentation, topical antibiotics and lubricants. Underlying refractive error, if any, should be treated.

Stye

Stye is an acute suppurative inflammation of glands of Zeis and Moll resulting in a painful deformity of eyelid margin at base

of cilia **(Fig. 7)**. It may be associated with cellulitis of the eyelid which can lead to abscess formation if left untreated. Treatment is by a combination of hot fomentation, antibiotics (topical and oral systemic), and analgesics. Underlying refractive error, if any, should be treated.

Chalazion

Chalazion is a nonsuppurative granulomatous inflammation of the meibomian gland. Blockage of meibomian gland duct causes collection of secretory material leading to a cosmetically unacceptable, painless swelling away from the lid margin **(Fig. 8)**. Larger lesions may cause astigmatism or get secondarily infected. Multiple chalazions require an investigation for uncorrected refractive error/immune compromise condition. Treatment in early stages is conservative with topical antibiotics with steroid combination and warm compresses. Definitive therapy is incision and curettage.

Pediculosis

Pediculosis is the infestation by lice (*Pediculosis capitis, Pediculosis pubis*) causing a blepharitis like presentation **(Fig. 9)**, diagnosed by slit lamp examination. Treatment options include trimming or plucking of eye lashes, malathion drops 1% or malathion shampoo 1%, and pilocarpine gel 4% application. Hygiene status and child neglect/abuse has to be checked out.

Figure 8 Chalazion right upper eyelid
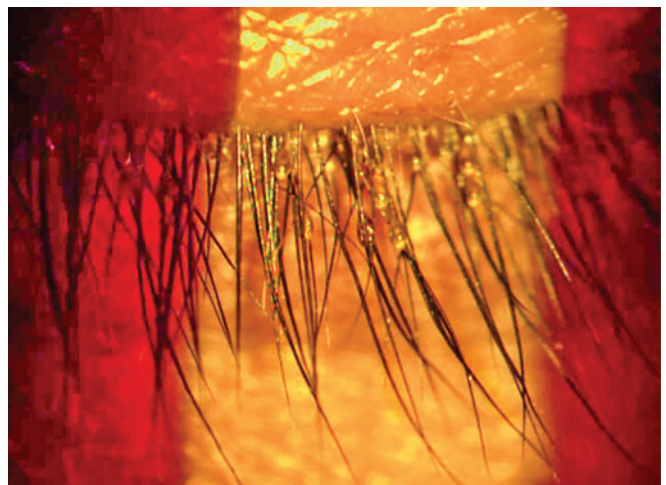
Figure 9 Eyelid pediculosis

DISORDERS OF THE ORBITS

Congenital Orbital Lesions

Developmental abnormalities of the orbit occur in isolation or as part of craniofacial disorders. The presentation varies from nonpulsatile or pulsatile proptosis to absent or small eyeball with or without associated abnormalities. Diagnosis is clinical, abetted by radiological investigations. Anophthalmos, congenital cystic eye, and microphthalmia have been already discussed in earlier chapters. Failure of closure of optic fissure superimposed with aberrant growth of tissues results in microphthalmia with cyst **(Figs 10A and B)**. The variably sized cyst presents under the lower eyelid. Treatment is dictated by age of the child, cyst size, visual potential, severity of microphthalmia, and associated abnormalities. Enucleation and cyst excision, cyst excision only, cyst aspiration with subsequent cyst excision and use of intracystic sclerosing agents have been described. Prosthetic rehabilitation is the goal of treatment.

Orbital Encephalocele

Failure of separation of surface ectoderm and neuroectoderm leads to a dehiscence in bone and protrusion of meninges (meningocele), brain tissue (encephalocele) or both (meningoencephalocele) through the defect. The trapped cerebrospinal fluid makes the pulsatile cyst transilluminant. The swelling presents in superior or superomedial quadrant of the orbit. Treatment consists of excision of the cyst and repair of bony defect.

Dermoid Cysts

Dermoid cysts arise from ectodermal rests trapped in suture lines, most frequently seen in superolateral quadrant, though they can occur at any suture line. Anteriorly placed are more common than posterior. Anterior dermoids present early as a painless, nonmobile, firm mass related to the orbital margin **(Fig. 11)**. Posterior dermoids cause proptosis **(Figs 12A and B)** and have a delayed presentation, with or without visual involvement. Treatment of dermoid cyst is surgical excision.

Craniofacial Anomalies

Both craniofacial dysostosis and mandibulofacial dysostosis are known to affect the orbit, due to restricted growth, in one or more axis (anteroposterior, lateral and vertical axis). Shallow bilateral orbits, result in proptosis associated with visual disturbance, hypertelorism and strabismus. Crouzon syndrome and Apert syndrome are examples of craniofacial anomalies. Treacher-Collins syndrome and Goldenhar syndrome are examples of mandibulofacial dysostosis. Treatment is complex, surgical correction is performed in association with plastic surgeons and neurosurgeons.

Inflammations of the Orbit

Orbital Cellulitis

The orbit is predisposed to infections due to anatomical characteristics of fenestrated thin walls and valveless superior and inferior ophthalmic veins. Chandler et al. modified classification of Smith and Spencer as Group I: Preseptal cellulitis, Group II: Orbital cellulitis, Group III: Subperiosteal abscess, Group IV: Orbital abscess and, Group V: Cavernous sinus thrombosis.

Infection from the face, nose and paranasal sinuses, soft palate, tonsils, teeth, and ears can act as a source for direct inoculation, extension from adjacent structures, and hematogenous spread of infection. Systemic manifestations of infection (fever, tachycardia) are associated with acute onset proptosis with painful restriction of external ocular movements and diminution of vision. Bilateral involvement and signs of meningeal irritation are indicators of intracranial spread. *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA) and *Streptococcus* species are the most common

Figure 11 Anterior dermoid in the superotemporal quadrant of the left orbit. Note the well circumscribed cystic lesion in the anterior left orbit

Figures 10A and B Microphthalmos associated with the cyst. (A) Frontal view; (B) Coronal section computed tomography (CT) scan
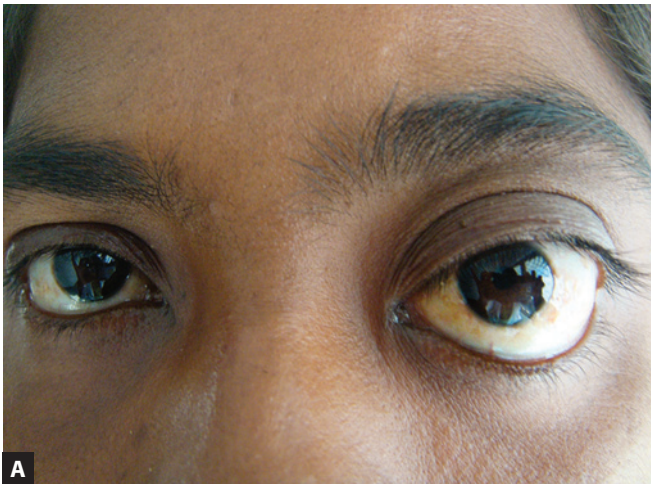
Figures 12A and B (A) Proptosis left eye due to a posterior dermoid. Note the cystic lesion present in the left orbit in association with the lateral orbit wall; (B) CT scan of the same patient

offenders. The patient should undergo hematological evaluation for general condition and radiological assessment (computed tomography [CT] scan/magnetic resonance imaging [MRI]) for localization and staging of infection **(Figs 13 and 14)**.

Treatment Urgent hospitalization to start intravenous therapy with broad spectrum antibiotic for aerobic and anaerobic organisms, instituted until infected eye appears nearly normal. Subsequently oral antibiotic therapy is continued to complete a 3-week course of therapy. Localized abscess should undergo drainage under antibiotic cover. Complications like exposure keratopathy, central retinal artery occlusion and cavernous sinus thrombosis need urgent management. Supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and nutritional supplements is added.

Parasitic Infestations

Cysticercosis and hydatid cysts are known to infest the orbit. Clinical presentation depends on site of involvement.

Cysticercosis usually presents as recurrent periocular swelling, with mild to severe proptosis with or without diplopia and ptosis.

There is partial response to oral steroids and NSAIDs. Cyst is identifiable on radiology (CT/MRI) and has been reported from all sites in the orbit **(Figs 15A and B)**. Treatment consists of oral albendazole (15 mg/kg/day) for 4 weeks under cover of oral corticosteroids (1.5 mg/kg/day in a tapering dose). The child must be monitored for seizures during albendazole therapy.

Orbital hydatid cyst (*Echinococcus granulosus*) presents as exophthalmos, chemosis, lid edema, visual impairment, and restriction of extraocular motility **(Figs 16A and B)**. Albendazole treatment is initiated 14–28 days prior to surgical excision of the cyst.

DISORDERS OF THE LACRIMAL SYSTEM

Congenital Lesions of Lacrimal System

Congenital Dacryocystocele (Mucocele, Amniotocele)

A variant of nasolacrimal duct obstruction (NLDO), it occurs due to failure of mesoderm to canalize distally combined with distal obstruction of NLD leading to a functional or mechanical proximal
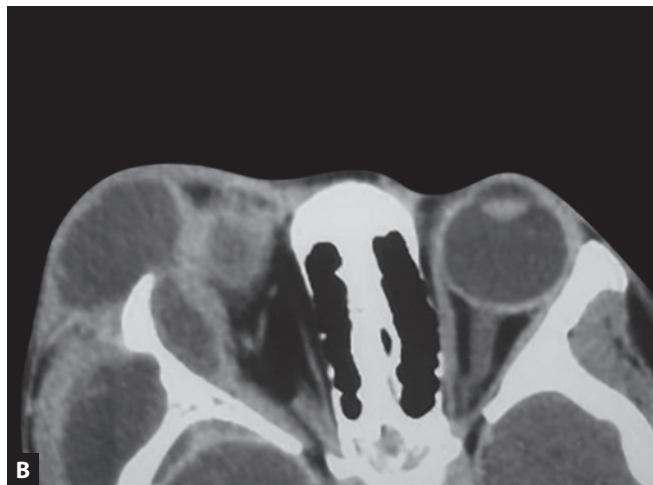
Figures 13A and B Orbital cellulitis, secondary to (A) eyelid abscess on right upper eyelid; (B) computed tomography (CT) scan shows diffuse infiltration of orbital tissues in the anterior orbit

Figure 14 Orbital cellulitis. Note the well defined abscess present in the left orbit and eyelid

obstruction. It presents as a bluish, cystic, firm mass below the medial canthus, shortly after birth, causing an upward slanting of the palpebral fissure nasally **(Fig. 17)**. Rarely, it may cause a cystic expansion into the nose. Dacryocystitis can develop within a few days or weeks and requires intravenous antibiotics to prevent life-threatening sepsis. Differential diagnosis includes encephaloceles, hemangiomas, dermoids, and nasal gliomas. Treatment is effected by probing and irrigation of the nasolacrimal system. The intranasal component requires marsupialization of the cyst wall.

Congenital nasolacrimal duct obstruction is the result of a blockage at the distal end of the nasolacrimal system at the valve of Hasner, resulting in epiphora. In infants 6 to less than 10 months of age, more than half of eyes with NLDO will resolve within 6 months with nonsurgical management. At first presentation, lacrimal massage is performed in office, in children below 1 year. Parents are educated regarding the technique of massage to be followed at home. Failed lacrimal massage is treated by probing, done under general anesthesia. This procedure can be repeated thrice, at
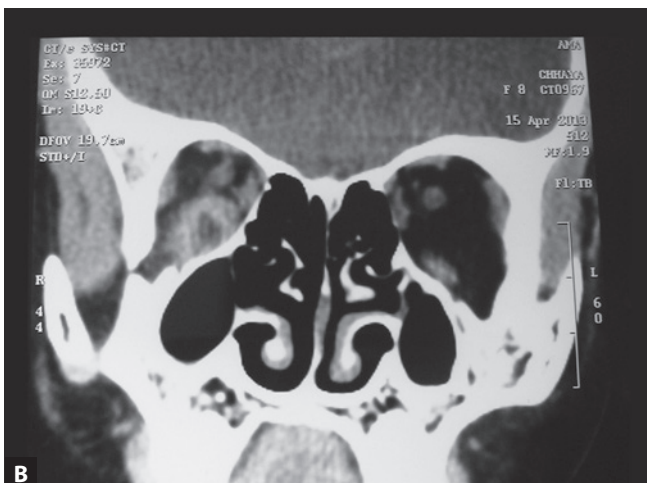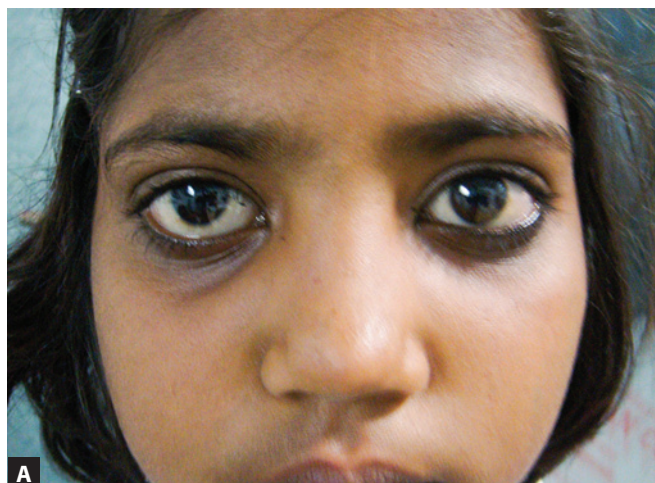
Figures 15A and B (A) Proptosis with hypertropia RE due to cysticercosis; (B) Note the inflammatory granuloma around the cyst in the right orbit coronal section computed tomography (CT) scan
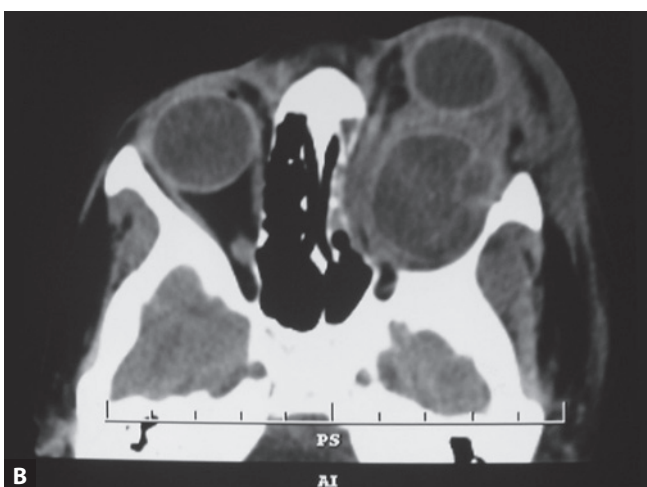
Figures 16A and B (A) Severe propotosis LE due to hydatid cyst; (B) Note the large cyst causing molding of the orbital walls

Figure 17 Amniotocele

intervals of 1 month. Silicone intubation or dacryocystorhinostomy or balloon dacryoplasty should be reserved for refractory cases. Acute dacryocystitis can occur as a complication in NLDO and is treated on the lines of preseptal cellulitis. Probing is withheld till the infection subsides.

MORE ON THIS TOPIC

Dutton JJ. Atlas of Clinical and Surgical Orbital Anatomy. 2nd edition. Philadelphia: Saunders; 2011.

Hornblass A. Oculoplastic, Orbital and Reconstructive Surgery. Baltimore, Maryland: Williams and Wilkins; 1990.

Rootman J. Diseases of the Orbit: a multidisciplinary approach. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2003.

Taylor D, Avetisov E. Pediatric Ophthalmology. Boston Oxford: Blackwell Scientific Publications; 1990.

Chapter 47.11
Ocular Injuries
Kalpana Narendran, Sandra C Ganesh

Ocular trauma is a major cause of ocular morbidity in children and is one of the important causes of noncongenital unilateral blindness in pediatric population. The spectrum of injuries ranges from trivial to potentially blinding. The consequent visual disability has a lasting impact on the child's future academic, financial and social prospects. Home and sports related injuries form the main bulk of the ocular injuries in children. Eye injuries cannot always be prevented but, it is possible to determine the most effective methods of reducing the incidence of visually damaging trauma, by identifying any underlying factors in the etiology of serious injuries. Pediatric eye trauma is a particular concern as the injured eye of the child is prone to develop vision deprivation amblyopia. Thus the time frame of visual rehabilitation after trauma is crucial to prevent permanent visual impairment in the child. In addition to the medicolegal aspect, the pediatrician should be alert to unnatural trauma as being part and parcel of child abuse.

EPIDEMIOLOGY

Boys are more vulnerable to trauma which is probably due to the more aggressive personality, more sporting activities and more out of home time spent by them. School aged children are the most susceptible age as they are unsupervised amongst their active peers than younger stay at home children. Injuries more commonly occur at home followed by school and playgrounds. Socioeconomic, sociocultural status and family supervision are important factors in determining ocular trauma in children. Ocular injuries are one of the common causes of absence of students from classes and it adversely affects the student's performance and educational opportunities.

ETIOLOGY

Causes of injuries are varied and no one pattern or cause can be identified in the curiosity driven, pleasure seeking and at times reckless childhood.

- *Birth trauma* occurs during forceps-assisted vaginal delivery can cause trauma to the cornea leading to corneal scar.
- *Domestic injuries* Accidental fall, blunt trauma with toys or household appliances, penetrating eye injuries with sharp objects are the frequent causes of ocular injuries in toddlers. Accidental blunt trauma is more common than penetrating eye injury with sharp objects. One of the common causes of preventable ocular trauma in children is unsupervised games like bow and arrow.
- *Fire cracker injuries* are more commonly encountered during festivals like *Diwali, Holi* and can lead to variable damage to ocular structures like lid tear, corneal tear, hyphema, traumatic cataract, globe rupture, retained intraocular foreign body.
- *Chemical injuries* by accidental entry of color into the eye need immediate irrigation of the eye. Accidental chemical injury, though not very common in children, is to be attended as ocular emergency. While almost any chemical can cause ocular irritation, serious damage generally results from either strongly basic (alkaline) compounds or acidic compounds. Exposure to lime powder or paste (*chunna*) is one of the commonly encountered chemical injuries. Bilateral chemical exposure is especially devastating, often resulting in complete visual disability. Immediate, prolonged irrigation of the eye should be done followed by application of antibiotic eye ointment and then patient should be referred to the ophthalmologist for aggressive early management and close long-term monitoring which is essential to promote ocular surface healing and to provide the best opportunity for visual rehabilitation.

CLASSIFICATION OF OCULAR INJURIES

Ocular injury occurs in three forms: (1) open globe, (2) closed globe, and (3) adnexal injuries.

- *Closed globe injury or nonpenetrating trauma* The eye globe is intact, but tears may occur in seven rings of the eye namely central iris: sphincter tear; peripheral iris: iridodialysis; anterior ciliary body: angle recession; separation of ciliary body from the scleral spur: cyclodialysis; trabecular meshwork: trabecular meshwork tear; zonules/lens: zonular tears with possible lens subluxation; separation of the retina from the ora serrata: retinal dialyses have been classically described as affected by blunt trauma.
- *Penetrating trauma* The globe integrity is disrupted by a full-thickness entry wound and may be associated with prolapse of internal contents of the eye. **Box 1** summarizes the referral guidelines for children with penetrating injuries.
- *Perforating trauma* A severe injury where globe integrity is disrupted in two places due to an entrance and exit wound (through and through injury).
- *Adnexal injuries* Blowout fracture of the orbit is caused by blunt trauma, classically described for fist or ball injury, leading to fracture of floor or medial wall of orbit due to sudden increased pressure on orbital contents. Fracture of orbital bones can lead to muscular entrapment limiting gaze in one direction.

Open globe injuries are one of the most common emergencies in ophthalmologic clinics and require immediate operation.

CLINICAL MANIFESTATIONS AND MANAGEMENT

Orbit and Eyelid Injuries

Lid Lacerations
Lid lacerations may be partial or full thickness and may involve the complex lacrimal drainage system. For superficial lacerations rinsing area with saline, cleaning wound with povidone iodine, and applying antibiotic eye ointment with sterile dressing suffices. Deeper lacerations require suturing in layers with 8-0 silk or nylon preferably by an oculoplastic surgeon **(Fig. 1)**.

Blow Out Fractures
The medial and inferior walls are most susceptible areas, with entrapment of orbital contents in adjacent sinuses. The main features include enophthalmos with limited ocular motility in affected region. Magnetic resonance imaging (MRI) orbit is investigation of choice however in cases with suspected metallic foreign bodies computed tomography (CT) orbits has to be done as MRI can dislodge the metallic foreign bodies by their

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BOX 1 Penetrating eye injury: Referral protocols

- Do not attempt to put pressure on eyes or to force the eyelids open as the intraocular contents can get extruded
- Do not try to remove any intraocular foreign body
- Ensure child remains nil orally from the time they are seen till they reach the ophthalmic facility
- Tetanus prophylaxis, systemic antibiotics and analgesics can be given

Figure 1 Lid tear

Figure 2 Blowout fracture

electromagnetic influences and cause greater damage to the surrounding structures **(Fig. 2)**. Management is mainly surgical for release of muscle entrapment or repair of orbital floor by orbitotomy after the edema and inflammation has settled approximately by a week's time.

Conjunctival Injuries

Subconjunctival hemorrhages can be managed conservatively by application of topical anti-inflammatory drops. Conjunctival tears may be accompanied by occult scleral tears. Small conjunctival tears can be managed conservatively with topical antibiotic drops and ointments. Large conjunctival tears associated with or without scleral tears require suturing. Intraocular foreign body should be ruled out before scleral tear repair is undertaken. Scleral perforations are associated with hypotony of globe with or without prolapse of vitreous and uveal tissue. In case of conjunctival tears, there is no hypotony as the scleral coat is intact.

Corneal Injuries

Abrasions are managed conservatively with antibiotic ointment and eye patch. It is important to inspect the fornices and evert lids to look for occult foreign bodies. Superficial foreign bodies can be removed with a moistened cotton tip applicator or a 26 G needle after topical anesthesia preferably under magnification (slit-lamp). To differentiate between a corneal abrasion and a corneal foreign body slit-lamp examination is necessary although sometimes if foreign body is large enough it can be seen on torch light examination with naked eye. An attempt to record vision in each eye should be made prior to referral. Lacerations-partial or full thickness, full thickness lacerations require suturing **(Fig. 3)**.

Scleral Injuries

Scleral lacerations may be associated with varying degrees of uveal and vitreous prolapse. Management is surgical by scleral tear repair after looking for any intraocular foreign body.

Anterior Chamber Injuries

Blood in the anterior chamber, may be associated with raised intraocular pressure (IOP). The goals of management are to normalize the IOP, prevent rebleeding and to reduce the inflammation. IOP is controlled by topical antiglaucoma medications. Rebleed occurs generally after 2–5 days during the stage of clot lysis and clot retraction. The clot can be stabilized by aminocaproic acid 50 mg/kg every 4 hourly given orally for 5 days. Topical steroids and atropine ointment are used to reduce inflammation. In cases of uncontrolled IOP, surgical evacuation of clot may be warranted. Traumatic iritis is managed by topical nonsteroidal anti-inflammatory drugs (NSAIDs) or weak steroids like loteprednol. Other injuries may result in traumatic mydriasis or iridodialysis **(Fig 4)**.
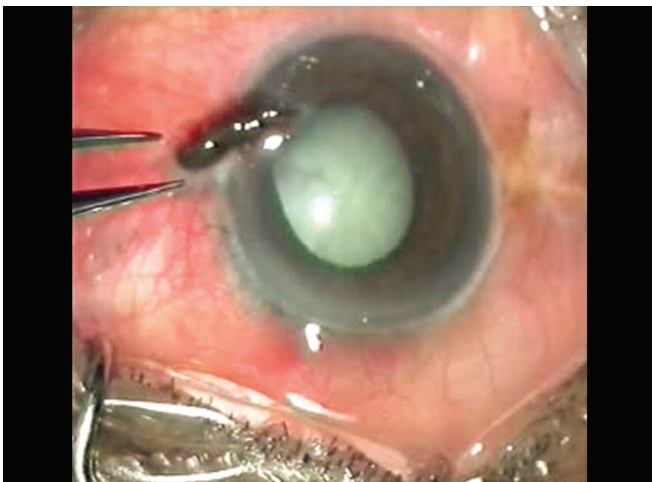
Figure 3 Corneal tear with iris prolapse and traumatic cataract
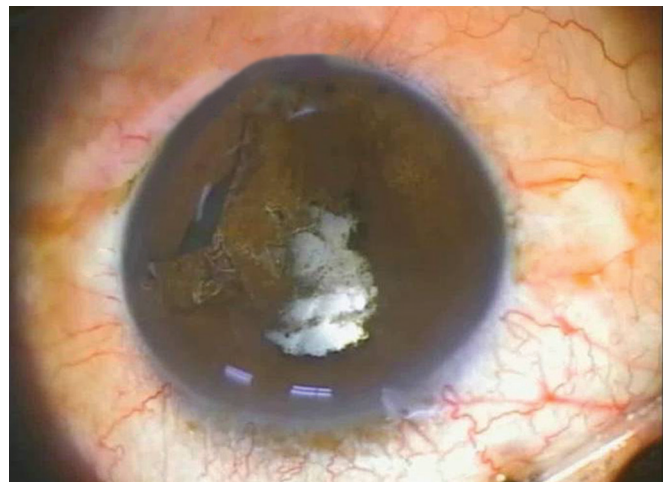
Figure 4 Traumatic cataract with iridodialysis

Lens Injuries

Traumatic Cataract (Fig. 5)

Rosette cataract is the typical cataract seen after concussion/blunt injury. It is a rapidly evolving cataract and is managed by performing appropriate cataract surgery. Other injuries include subluxation (partial displacement of lens) or dislocation or luxation (significant structural displacement). Indication for primary cataract extraction includes ruptured anterior lens capsule with lens matter in anterior chamber; or posterior segment complications like retinal detachment, endophthalmitis or retained intraocular foreign body. In the absence of the earlier situations the cataract extraction is done after the inflammation subsides after few weeks or months. The surgery for traumatic cataract is followed by optical correction, i.e., glasses or contact lenses and amblyopia treatment.

Posterior Segment Injuries

Loss of red glow of fundus on distant direct ophthalmoscopy in absence of corneal pathology and dense cataract is an indicator of posterior segment involvement. In presence of corneal opacity or dense cataract, B-scan ultrasonography is required to look for posterior segment involvement. If posterior segment involvement is suspected then an emergent ophthalmic consultation is to be emphasized to the parents especially in suspected intraocular infection (endophthalmitis). Signs of endophthalmitis would be vision loss out of proportion to the injury extent, persisting redness of conjunctiva, yellow or white reflex of fundus, irritable child and decreased IOP.

- *Vitreous hemorrhage* Small vitreous hemorrhage is managed conservatively. Dense vitreous hemorrhage requires vitrectomy at a later date once posterior vitreous detachment has occurred and ocular inflammation has resolved.
- *Retinal dialysis/tears* They are managed by *Barrage laser* to prevent subsequent retinal detachment **(Fig. 6)**.
- Retinal edema also known as *Berlins edema* and hemorrhage can be seen. This is managed conservatively and vision gradually normalizes as retinal edema subsides. However, sometimes it may be associated with subnormal vision **(Fig. 7)**
- *Choroidal and retinal detachment* Traumatic retinal detachments require surgical intervention.
- *Optic nerve avulsion* **(Fig. 8)** presents with sudden total visual loss with nonreacting pupil. Retinal examination reveals a hole or cavity where the optic disc has retracted into its dural sheath.
- *Traumatic optic neuropathy* If detected early is treated by high dose intravenous methylprednisolone. Surgical decompression of optic nerve is done in cases of optic canal fracture with fracture chip of bone impinging on optic nerve. Prognosis is variable and depends on the extent of initial injury and the time delay between injury and seeking appropriate treatment **(Fig. 9)**.
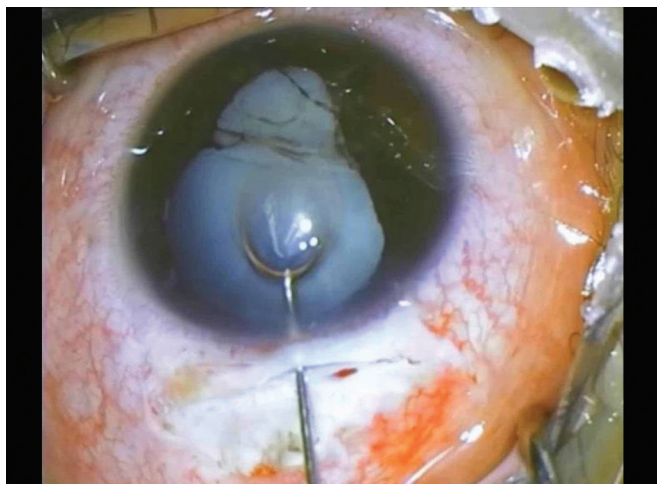
Figure 5 Traumatic cataract with ruptured anterior capsule
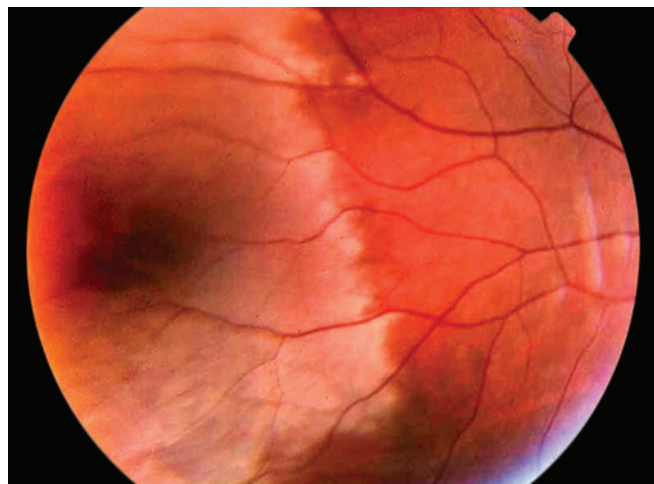
Figure 7 Berlins edema
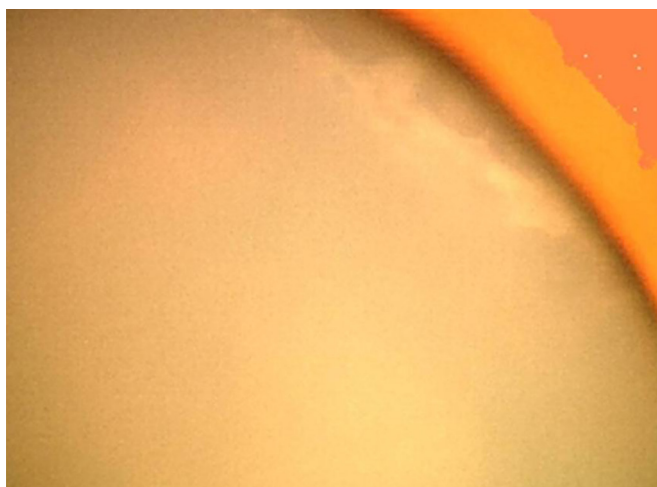
Figure 6 Retinal dialysis
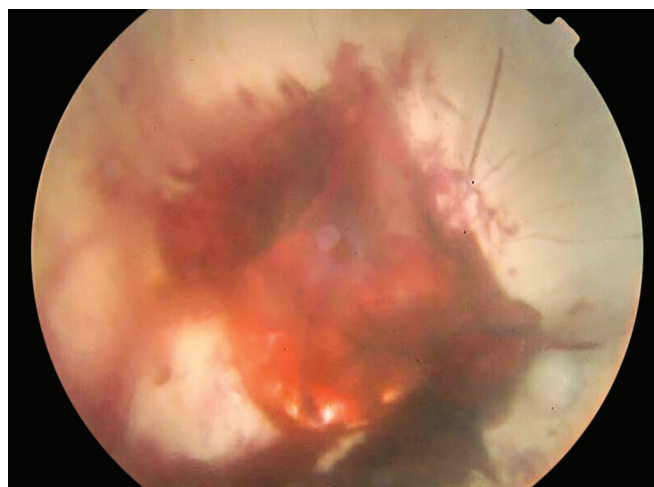
Figure 8 Optic nerve head avulsion
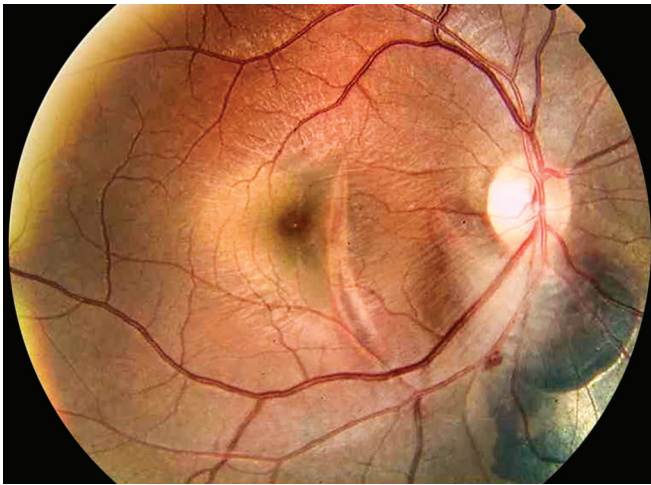
Figure 9 Choroidal rupture

Figure 10 Traumatic avulsion of superior rectus muscle following fishhook injury

Muscle Injuries

These can be subdivided as isolated muscle trauma **(Fig. 10)**, nerve palsies, and orbital fracture with muscle entrapment. Distinguishing between isolated muscle trauma and nerve palsies requires expert opinion preferably from a strabismologist. Orbital fracture with muscle entrapment should be suspected if there are signs of severe injury to the orbit with enophthalmos and restriction of elevation or adduction in the affected eye. On Water's view radiograph, polypoid mass can be observed *hanging* from the floor classically known as teardrop *sign,* as it usually is in shape of a teardrop.

INTRAOCULAR FOREIGN BODIES

Foreign bodies may damage the eyes by virtue of mechanical damage during impact and toxic reactions to the substance. Vegetable matter is notorious for causing fulminant reaction and endophthalmitis. Certain specific manifestations like siderosis and chalcosis are also recognized.

Siderosis bulbi is caused by the toxicity of ionized iron particles liberated from an intraocular iron-containing foreign body. Corneal stromal pigmentation, iris heterochromia, pupillary sphincter damage, rust brown lens deposits and retinal degeneration due to ferrous and ferric ions comprise the spectrum of the condition. The latter contributes to irreversible vision loss.

Chalcosis refers to intraocular copper deposition, which may be recognized as acute or chronic. Acute chalcosis manifests as sterile endophthalmitis with retinal detachment and is caused by foreign bodies with high copper content (> 85%). Kayser-Fleischer (KF) ring, sunflower cataract and iris heterochromia can also occur, mostly in association with chronic chalcosis wherein the offending agent is low on copper content (< 85%). Thus foreign bodies with copper or iron content must be removed at all cost as early as possible.

Management includes localization and prompt removal of the foreign body by pars plana vitrectomy with or without of lensectomy, using magnets or forceps. Imaging like CT scan and ultrasound B-scan are useful for localization of intraocular foreign body. MRI is contraindicated in suspected metallic foreign bodies.

APPROACH TO PATIENT

Good history taking is of utmost importance from parents and child keeping in mind that the child and the parents can conceal the history when either of them is at fault. The documentation should be meticulous since some of these cases can be of medicolegal importance. The ocular examination should include:

- Age-appropriate vision assessment
- Pupil responses, especially for a relative afferent defect
- External eye inspection, including lids, ears, and face
- *Refraction* To find best corrected visual acuity
- Slit-lamp examination if possible, looking for iridodonesis, pupil sphincter rupture, cataract, and subtle hyphema. Portable slit-lamp may be used if required
- IOP recording and gonioscopy if child is cooperative
- Fundus examination with the pupil dilated including indirect ophthalmoscopy
- Documentation of clinical findings with relevant drawings
- Fundus photography and external photography.

A child with suspected perforation should be referred to ophthalmologist with IV line open and advise the parents to keep the child fasting so that treatment under general anesthesia, if needed can be initiated immediately once the child reaches the ophthalmologist.

PROGNOSIS

Children are not aware of the consequences of eye injury and often report the injury after substantial damage has already occurred. This leads to delayed medical and surgical intervention and ultimately poor visual outcome.

The major prognostic factors include extent of primary injury; time interval between injury and seeking medical advice; superadded infection; coexistent glaucoma; and posterior segment complications like post-traumatic endophthalmitis, traumatic optic neuropathy, severe Berlins edema and optic nerve avulsion. The overall prognosis for patients with ocular trauma remains guarded. These patients should be followed-up at regular intervals and monitored closely for any visual deterioration which can be due to rise in IOP and resulting optic nerve damage years after the actual injury. The prognosis for posterior segment complications

like post-traumatic endophthalmitis, traumatic optic neuropathy and optic nerve avulsion remain poor inspite of aggressive treatment.

PREVENTIVE STRATEGIES

Most ocular injuries are preventable. Health promotion is the key intervention needed. Public awareness needs to be created regarding discouraging children from playing with bow and arrow or any other sharp things. Parents should closely monitor their children at all times at home as well as during playtime. Use of eye protective glasses while playing outdoor sports involving high speed projectiles can prevent almost 90% of sports related injuries. Polycarbonate glasses are unbreakable and are available in most of the optical shops. Missile firing toys and guns should be avoided.

Age appropriate toys should be given to children. All chemicals and sprays should be kept out of reach of children. Use of sharp objects by children should be closely supervised. Playing with fireworks is to be totally discouraged. Festival related injuries can be avoided by safe playing with *Holi* colors and *Diwali* firecrackers.

MORE ON THIS TOPIC

Abbott J, Shah P. The epidemiology and etiology of pediatric ocular trauma. Survey Ophthal. 2013;58:476-85.

Kaur A, Agrawal A. Paediatric ocular trauma. Current Science. 2005;89: 1.

MacEwen C, Baines P, Desai P. Eye injuries in children the current picture. Br J Ophthalmol. 1999;83:933-6.

Desai T, Vyas C, Desai S, et al. Pattern of ocular injury in pediatric population in western India. NHL Journal of Medical Sciences. 2013:2:37-40.

Chapter 47.12
Ocular Manifestations of Systemic Disorders
Koushik Tripathy, Pradeep Venkatesh

Systemic conditions frequently manifest some ocular features. In this section, we discuss some of the systemic conditions in children that have manifestations in the eye.

VITAMIN DEFICIENCIES

Xerophthalmia is defined as ocular manifestations of vitamin A deficiency, including the structural changes of conjunctiva, cornea and retina, and changes in functions of retinal rods and cones. Details are available in the specific chapter on vitamin A deficiency in the Section on Nutrition. Xerophthalmic fundus (Uyemura fundus) is characterized by typical seed-like, raised, whitish lesions at equator of retina, which disappear after vitamin A therapy. Ocular manifestations of deficiency of other vitamins are as follows: optic neuropathy, angular blepharoconjunctivitis (B_2); gyrate atrophy (B_6); flame-shaped hemorrhage (B_{12}); Vitamin C (subconjunctival hemorrhage, orbital hematoma); Vitamin K deficiency (ocular hemorrhage); and Vitamin D deficiency (cataract).

INFECTIONS

Bacterial Infections

Tuberculosis
The most common ocular presentation is as posterior uveitis. The ocular manifestations may be anterior uveitis which is typically granulomatous associated with mutton fat keratic precipitates, and iris nodules; ciliary body tuberculoma; intermediate uveitis, nodular scleritis, posterior uveitis and panuveitis. Posterior segment features are choroidal tubercle, choroidal tuberculoma, and serpiginous like choroiditis, multifocal choroiditis, subretinal abscess, cystoid macular edema, and exudative retinal detachment. It may also present as retinitis and retinal vasculitis, neuroretinitis, optic nerve infiltration, endogenous endophthalmitis and panophthalmitis. Tuberculosis may also present as granuloma or cold abscess in orbit and ocular adnexa.

Leprosy
The anterior segment of the eye, which is cooler than posterior segment, is most commonly affected by leprosy especially lepromatous type. The most common ocular presentation is chronic anterior uveitis characterized by iris nodules, iris pearls, posterior synechia, iris atrophy, and miotic pupil. The ocular features may be madarosis, lagophthalmos, chronic dacryocystits, entropion of upper eyelid, blepharochalasis, trichiasis, superficial punctate keratitis, prominence and beading of corneal nerves (corneal anesthesia), interstitial keratitis, corneal ulcers, chronic conjunctivitis, lepromatous conjunctival nodules, erythema nodosum leprosum, pterygium, chronic anterior uveitis, cataract (due to uveitis or steroid used in lepra reaction), scleritis, and episcleritis.

Pertussis
Patient may present with subconjunctival hemorrhage.

Gradenigo Syndrome
This is a manifestation of inflammation of petrous apex (petrous apicitis) due to otitis media and mastoiditis involving the apex of the petrous temporal bone. The classical triad consists of periorbital unilateral pain due to trigeminal nerve involvement, diplopia due to sixth nerve palsy and persistent otorrhea.

Cat Scratch Disease
Eye may be involved in up to 26% of systemic *Bartonella* infection (cat scratch disease). The ophthalmic manifestations are neuroretinitis (disc edema and macular star), serous macular detachment, focal chorioretinitis, optic neuritis, acute multifocal inner retinitis or a characteristic retinal white spot syndrome, Bartonella retinitis, focal choroiditis, optic nerve granuloma, anterior uveitis, vitritis, pars planitis, focal retinal vasculitis, branch retinal arteriolar and venular occlusions, retinal vasculitis and peripapillary angiomatosis. Up to 7% cases of cat scratch disease develop neurological complications like encephalitis, aseptic meningitis, seizures, transverse myelitis, cerebral vasculitis or abscess, peripheral neuropathy, polyneuritis or radiculitis and Bell's palsy. It occurs from a scratch or bite of an infected kitten or cat. The cat fleas (*Ctenocephalides felis*) carry *Bartonella henselae* in intestinal tract and excrete the organism in their feces. Cat scratch disease usually presents as self-limiting lymphadenopathy over 3–6 weeks in immunocompetent individuals. Cat scratch disease is treated by systemic penicillin, cephalosporins, doxycycline, erythromycin, rifampin, azithromycin, or ciprofloxacin.

Congenital Syphilis
The ocular manifestations of congenital syphilis are limbitis with cherry red limbal congestion with deep stromal vessels with corneal clouding (Salmon patch), intracorneal bleed, granulomatous anterior uveitis, ghost vessels, orbital periostitis, nasolacrimal duct stenosis, dacryoadenitis, papular skin rash of the eyelids, mucous patches of the conjunctiva, congenital cataract, glaucoma, chorioretinitis, chorioretinal scarring, and optic atrophy. In acquired primary syphilis, chancres may be seen at adnexa and conjunctiva. Secondary syphilis presents orbital periostitis, maculopapular rash of the eyelid skin, papillary conjunctivitis, episcleritis, marginal keratitis, granulomatous or non-granulomatous anterior uveitis, iris roseolae, lens subluxation, vitritis, diffuse or localized choroiditis or chorioretinitis, disc edema, exudative retinal detachment, neuroretinitis, retinal vasculitis, chorioretinal scars, optic neuritis, and optic perineuritis.

Fungal Infections
Candida albicans causes infections usually in immuno-compromised children. The ocular manifestations may be corneal ulcer, endogenous endophthalmitis, subretinal abscess or lens abscess especially in septic premature infants.

Viral Infections

Herpes Simplex Virus
Congenital or neonatal herpes simplex virus (HSV) infection manifests as conjunctivitis, keratitis, and chorioretinitis. Other ocular features are microphthalmos, cataract, and optic atrophy. Primary infection, without previous viral exposure, usually occurs in childhood and manifests as blepharitis, follicular conjunctivitis, herpetic vesicles at eyelid, and preauricular lymphadenopathy. Both systemic and ocular manifestations of primary HSV infection are mild and self-limiting. Primary HSV infection may also present as epithelial keratitis (superficial punctate keratitis, dendritic keratitis, or geographic keratitis). Recurrent herpes virus infection presents as stromal keratitis, endotheliitis or disciform keratitis, iridocyclitis, elevated intraocular pressure, and retinitis (acute retinal necrosis). Skin and conjunctival involvement is less common in recurrent HSV infection. The resultant corneal opacity may lead to amblyopia.

Measles

Ocular manifestations may be corneal epithelial keratitis, Koplik's spots on conjunctiva, optic neuritis, retinal vascular occlusions and pigmentary retinopathy. Measles keratopathy is a common cause of childhood blindness in the developing world. The keratitis is bilateral and starts in the peripheral cornea. It may result in severe complications like corneal ulceration, perforation, leukoma, endophthalmitis, and phthisis. Sudden bilateral vision loss due to measles retinitis may occur 1–2 weeks after the onset of the rash. It is characterized by macular edema, neuroretinitis, disc edema, attenuated arterioles, and retinal hemorrhages. Eye is involved in almost 50% of children with subacute sclerosing panencephalitis (SSPE). Common features are maculopathy with retinal pigment epithelial changes and focal retinitis. Other ocular manifestations are disc edema, papillitis, optic atrophy, serous retinal detachment, chorioretinitis, retinal hemorrhage, retinal folds, hemianopsia, nystagmus, and cortical blindness.

Rubella

Congenital rubella syndrome (Gregg syndrome) is characterized by the triad of cataracts, deafness, and cardiac defects. Cataract is seen in about 15% cases which may be nuclear cataract with pearly appearance or total cataract. Mild microphthalmia with hypermetropia is commonly associated. Other ocular manifestation are salt and pepper retinopathy, microcornea, microphthalmos, glaucoma, keratitis, anterior uveitis, iris atrophy, refractive errors, nystagmus, and strabismus. The salt and pepper retinopathy is the most common ocular feature (24–62%), which typically does not affect vision unless complicated by choroidal neovascularization. Ocular manifestations of acquired rubella are nonpurulent conjunctivitis, epithelial keratitis, retinitis, and exudative retinal detachment.

Varicella Zoster Virus

Varicella most commonly presents as papillary conjunctivitis and conjunctival vesicle formation. Other ophthalmic features include epithelial keratitis (punctate or dendritic), subepithelial infiltrates, stromal keratitis, disciform keratitis, nongranulomatous anterior uveitis, internuclear ophthalmoplegia and oculomotor palsy. Most common ocular feature of congenital varicella is chorioretinitis. Herpes zoster ophthalmicus (HZO) presents as maculopapular eruption which later form vesicles over dermatome supplied by ophthalmic nerve. Hutchinson sign is involvement of the skin supplied by the external nasal nerve, a branch of the nasociliary nerve supplying the tip, side and root of the nose. The sign correlates strongly with ocular involvement although there is no correlation between the severity of the rash and the severity of ocular complications. Other features are cranial nerve palsy, dermatitis of the eyelids, stenosis of the lacrimal puncta, follicular conjunctivitis, episcleritis, and scleritis, epithelial keratitis (pseudodendrites, punctate epithelial keratitis) or stromal keratitis (anterior stromal infiltrates), endotheliitis, neuro-trophic keratitis, iridocyclitis, glaucoma, optic neuritis, acute retinal necrosis, and in immunocompromised patients progressive outer retinal necrosis syndrome (PORN).

Molluscum Contagiosum

It is a common DNA pox viral infection contracted by direct contact or via fomites. Characteristic discrete nodular lesions are approximately 2–4 mm and with a central umbilication and an underlying pearly white material that can be expressed but contains active virus. Lid margin involvement can lead to chronic ocular irritation due to virus shedding into the conjunctival sac with chronic follicular blepharoconjunctivitis, superficial punctate keratopathy, and conjunctival molluscum lesions.

Parasitic Infections

Toxocariasis

It is caused by the dog intestinal roundworm *Toxocara canis*, or the cat roundworm *Toxocara catis*. Ocular toxocariasis is caused by the second-stage or third-stage larva of the nematode. Most commonly ocular toxocariasis presents before 16 years of age. Typical manifestations are chronic endophthalmitis, posterior pole granuloma, and peripheral granuloma. Chronic endophthalmitis presents with leukocoria or squint or unilateral vision loss, anterior uveitis, hypopyon, posterior synechiae, cyclitic membrane, vitritis, peripheral granuloma, pars plana exudates and retinal detachment. The most common presentation is a unilateral granuloma of the posterior pole or peripheral retina. The posterior pole granuloma is typically round, elevated, and up to two disc diameters in size, with vitritis, vitreoretinal tractional band, and localized tractional retinal detachment. Peripheral granuloma presents late with vision loss due to macular distortion or retinal detachment with white hemispherical peripheral lesion associated with a vitreous band causing disc drag.

Toxoplasmosis

Cat is the definitive host of *Toxoplasma gondii*, an obligate intracellular protozoon. Intermediate hosts include mice, livestock and humans. Only tachyzoite among the three developmental forms (sporozoite, bradyzoite, and tachyzoite) induce inflammation and tissue destruction. Humans get infected transplacentally, after ingestion of meat of intermediate hosts (bradyzoites), or cat litter (sporocysts containing sporozoites). Mothers who contracted infections before conception do not transmit infection transplacentally. Congenital toxoplasmosis presents at birth as hydrocephalus, intracranial calcification, bilateral macular scars, and anophthalmos. Ocular features of acquired toxoplasmosis is toxoplasma retinitis, which is unilateral focal necrotizing retinochoroiditis, adjacent to old scar with dense vitritis giving rise to the *headlight in the fog* appearance, with vasculitis. *Spill-over* anterior uveitis, which may be granulomatous and resemble Fuchs syndrome, is common. Other features are punctate outer retinal toxoplasmosis, neuroretinitis, and papillitis. The retinitis is due to reactivation at previously inactive cyst-containing scars although in a small minority may represent new infection. In acquired immune deficiency syndrome (AIDS) toxoplasma retinitis lesions are larger, bilateral with minimal vitritis, multiple lesions, and confluent areas of retinitis resembling viral retinitis. It may be associated with cerebral or disseminated toxoplasmosis in AIDS.

Human Immunodeficiency Virus

Most common ocular finding in human immunodeficiency virus (HIV) infected children is retinal vasculitis of indeterminate etiology. Other manifestations include HIV retinopathy with retinal hemorrhages, microaneurysms and cotton wool spots, opportunistic infections (Cytomegaloviral [CMV] retinitis, acute retinal necrosis [ARN] due to HSV or varicella zoster virus [VZV], toxoplasma retinochoroiditis, syphilitic chorioretinitis, *Pneumocystis jirovecii* choroiditis, *Cryptococcus neoformans* choroiditis, and tuberculoma), Kaposi sarcoma, lymphomas involving the retina (primary intraocular lymphoma), adnexal structures, and orbit, herpes zoster ophthalmicus, molluscum contagiosum and squamous cell carcinoma of the conjunctiva. CMV retinitis typically occurs when CD4 counts drop below 50/μL.

CHROMOSOMAL DISORDERS

Cri-du-Chat Syndrome (5p)

Upward or downward slanting of the palpebral fissures, hypotelorism or hypertelorism, epicanthus, ptosis, myopia,

reduced tear production, strabismus, cataracts, glaucoma, tortuous retinal vessels, foveal hypoplasia, optic atrophy and colobomatous microphthalmia.

Trisomy 13 (Patau Syndrome)

Most common ophthalmic feature is iris or iridofundal coloboma. Other features include microphthalmia, cyclopia, cataract, corneal opacity, glaucoma, persistent hyperplastic primary vitreous, intraocular cartilage, optic nerve hypoplasia, and retinal dysplasia.

Trisomy 18 (Edwards Syndrome)

The most common ophthalmic anomalies include epicanthus, hypertelorism, and hypoplastic supraorbital ridges. Other features are blepharophimosis, ptosis, corneal opacity, congenital glaucoma, cataract, microcornea, retinal depigmentation, colobomatous microphthalmia, and cyclopia.

Trisomy 21 (Down Syndrome)

The ocular features include epicanthus, upward slanting of the palpebral fissures (Mongoloid slant), almond-shaped palpebral fissure, myopia, strabismus, nystagmus, blepharitis, ectropion of the eyelids, keratoconus, Brushfield spots of the iris, infantile glaucoma, blue sclera, eccentric pupils, congenital or acquired cataracts, color blindness, pigmentary disturbances of retina, and an increased number of retinal vessels crossing the disc margin.

Turner Syndrome

Ptosis and strabismus are the most frequently seen. Other features are cataract especially in patients with diabetes, refractive errors, corneal scars, blue sclera, and color blindness.

Klinefelters Syndrome

The ocular features are epicanthal folds, hypertelorism, and upward slant of palpebral fissures, strabismus, Brushfield spots, myopia, choroidal atrophy, and colobomatous microphthalmia.

CHILD ABUSE

Physical abuse may present as multiple unexplained fractures, periorbital ecchymosis, ocular burns, hyphema, and corneal abrasion. Retinal hemorrhages are the characteristic and most common ocular manifestation of shaken baby syndrome. Other features of shaken baby syndrome are preretinal, subinternal limiting membrane or vitreous hemorrhage, traumatic retinoschisis, Purtscher retinopathy, commotio retinae, and optic atrophy. Optic atrophy is the second most common cause for vision loss in shaken baby syndrome. Sexual abuse may manifest as sexually transmitted disease (AIDS, CMV retinitis, molluscum, pubic lice infection of eyelids).

Munchausen syndrome by proxy (factitious disorder by proxy), is a form of child abuse in which a parent, almost always the mother, engages in behaviors that result in the appearance of an illness in her otherwise well child usually of preverbal age. Ocular features are pupillary abnormalities due to covert poisoning or topical medication instillation, corneal scarring due to instillation of noxious chemicals, or orbital cellulitis due to the periocular injection of foreign materials.

CRANIOFACIAL ABNORMALITIES

Crouzon Syndrome

It is an autosomal dominant disorder caused by premature fusion of the coronal and sagittal sutures. Typical facial finding is midfacial hypoplasia and curved *parrot-beak* nose resulting in *frog-like* facies

and mandibular prognathism. Ocular features include proptosis due to shallow orbits (exorbitism), hypertelorism, *V* exotropia, ametropia and amblyopia. Vision-threatening complications include exposure keratopathy, globe luxation and optic atrophy, due to chronic papilledema and cerebral hypoperfusion secondary to sleep apnea. Ocular associations include ocular muscle abnormalities, recurrent dacryocystitis, blue sclera, megalocornea, keratoconus, cataract, ectopia lentis, glaucoma, vitreous opacities, coloboma, and optic nerve hypoplasia.

Apert Syndrome

Apert syndrome is the most severe of the craniosynostoses and may involve all the cranial sutures. Systemic features are like Crouzon syndrome except Apert syndrome patients have syndactyly, several visceral anomalies, and 30% patients have developmental delay. Ocular findings are shallow orbits, proptosis and hypertelorism (less pronounced than in Crouzon syndrome), exotropia, downward slant of the palpebral apertures. Ocular associations include keratoconus, ectopia lentis, albinotic appearance of fundus and congenital glaucoma.

Other craniosynostoses like Pfeiffer syndrome, Carpenters syndrome (a variant of Apert syndrome) have similar ocular findings.

Mandibulofacial Dysostosis (Treacher Collins, Franceschetti-Zwahlen-Klein Syndromes)

It is characterized by malformation of derivatives of the first and second branchial arches. Typical features include lower lid coloboma, lack of development of the malar bone and mandible; antimongoloid slant of the palpebral fissures, beaked nose, micrognathia, macrostomia, highly arched palate, anomalies of dentition, malformations of the external and middle ear, conductive deafness, atypical hairline with projections toward the check; and blind fistulas between the ears and angles of the mouth. Ocular features are antimongoloid slanting of the palpebral apertures, lower lid coloboma, astigmatism, cataract, microphthalmos, and atresia of the lacrimal passages. Rare manifestations include upper eyelid colobomas, corneal guttata, and ptosis.

Oculo-auriculo-vertebral Spectrum (Hemifacial Microsomia, Goldenhar Syndrome)

Characteristic findings are hypoplasia of the malar, maxillary and mandibular regions, macrostomia and microtia, preauricular and facial skin tags, cervical hemivertebrae, and mental handicap especially seen with microphthalmos. Most characteristic ocular finding is epibulbar (limbal) dermoid and conjunctival lipodermoids. Limbal dermoids are smooth, soft, yellowish, subconjunctival lesions, at the inferotemporal limbus showing protruding hair. Histopathology shows a solid mass of collagenous tissue containing dermal elements covered by stratified squamous epithelium. Other features are ptosis or narrow palpebral fissure, upper lid notching or coloboma, refractive error, amblyopia, microphthalmos, strabismus, Duanes retraction syndrome, corneal anesthesia, corneal ulcer, iris coloboma, uvea coloboma, and disc coloboma. Duane retraction syndrome may be associated with *Klippel-Feil anomaly* (cervical fusion, short neck, and posterior hairline) and *Wildervanck syndrome* (Klippel-Feil anomaly with sensory neural hearing loss).

Fetal Alcohol Syndrome

Maternal alcohol abuse during pregnancy can lead to blepharophimosis like picture, telecanthus, epicanthal folds, long eyelashes, anterior segment dysgenesis (posterior embryotoxon to a severely ectatic opaque cornea), microphthalmia, refractive

errors, strabismus, tortuous retinal vessels, optic nerve hypoplasia, and persistent hyaloidal vessels.

Hallermann-Streiff Syndrome (François Dyscephalic Syndrome, Oculomandibulodyscephaly)

Characteristic features of this sporadic disorder are frontal prominence, small beaked nose, baldness, progeria, micrognathia, pointed chin, short stature, hypodontia and narrow upper respiratory airway. Ocular features are cataract in 90% of cases, which may be membranous or may absorb spontaneously, microphthalmos, nystagmus, strabismus, and glaucoma. Less common features are blue sclera, uveitis, sparse eyebrows and eyelashes, downslanted palpebral fissures, iris atrophy, and disc coloboma.

Waardenburg Syndrome (Klein-Waardenburg Syndrome)

It is characterized by developmental anomalies of the eyelids, nasal root, and eyebrows, along with heterochromia iridis, white forelock, and sensorineural deafness. Telecanthus usually with further displacement of lacrimal puncta is typical finding. Other features are hypertelorism (10%), synophrys, partial or complete heterochromia of one or both iris, albinotic fundus, strabismus, cataract, microphthalmia, and ptosis.

CONNECTIVE TISSUE DISORDERS

Marfan Syndrome

It is an autosomal dominant disorder caused by mutation of fibrillin gene (FBN, chromosome 15q21). Fibrillin, seen in peripheral and equatorial areas of the normal lens capsule, plays a role in accommodation. Ectopia lentis, with bilateral lens subluxation superotemporally, stretched but intact zonules, and intact accommodation is diagnostic. It is seen in up to 80% cases. Unlike homocystinuria, crystalline lens dislocation either to anterior chamber or into vitreous is rare. The lens is microspherophakic in 15% cases adding to the myopia already present. Marfan syndrome without ectopia lentis is associated with a mutation in chromosome 3p24.2–p25. Other ocular features are flat cornea (20%), megalocornea, keratoconus, thin velvety poorly dilating iris with hypoplastic dilator pupillae, irregularly deep anterior chamber and iridodonesis due to subluxated lens, peripheral iris transillumination (10%), glaucoma (8%) due to congenital angle anomaly, pupillary block from anteriorly dislocated lens, phacolytic glaucoma from anteriorly dislocated mature cataract, and primary open angle glaucoma; myopia, early onset of cataract, retinal detachment (up to 25%), peripheral retinal degenerations like lattice, retinoschisis, retinal holes, and white without pressure, strabismus (exotropia in 10% and esotropia in 2%), and strabismic or anisometropic or ametropic amblyopia. Subluxated lens can result in high astigmatism if lens margin comes in pupillary area, requiring lens extraction.

Homocystinuria

It is an autosomal recessive condition due to decreased hepatic activity of cystathionine beta-synthase and systemic accumulation of homocysteine and methionine (chromosome 21q.22.3). However, it may also be caused by impaired activity of 5-methyltetrahydrofolate-homocysteine methyl transferase. Characteristic ocular feature is ectopia lentis inferonasally, is seen in 38% of untreated patients at 5 years age and in all patients by the age of 25 years. The zonule normally contains high levels of cysteine which in deficient in homocystinuria. In homocystinuria zonules disintegrate resulting in lost accommodation. Anterior dislocation of lens is common. Other ocular features include corneal opacity, cataract, iris atrophy, optic atrophy, myopia, cystic and pigmentary changes in retinal periphery, and retinal detachment. In patients with anterior dislocation of lens, dilation and supine position to return lens to posterior chamber is done, followed by pilocarpine therapy to constrict pupil and laser peripheral iridectomy. Because of the risk of thromboembolic phenomena with general anesthesia and the complications of surgery (retinal detachment, vitreous hemorrhage, and glaucoma), conservative management of the dislocated lens is preferred.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) VI (ocular sclerotic), is an autosomal recessive disorder of collagen caused by deficiency of procollagen lysyl hydroxylase (chromosome 1p36.3–p36.2). Of eleven distinct subtypes of EDS, type VI and, rarely, type I, and VII, are associated with ocular features. Systemic features of ocular sclerotic EDS are hypotonia in infancy followed by severe scoliosis, recurrent joint dislocations and stretchable skin, and high risk for catastrophic arterial rupture. Ocular features include blue sclera, scleral fragility with globe rupture caused by mild trauma, epicanthic folds, microcornea, keratoconus, keratoglobus, ectopia lentis, myopia and retinal detachment. Type I EDS (gravis) may present with stretchable lids and retinal detachment. Ocular features of type VII EDS (dermatosparaxis) are hypertelorism and epicanthus.

Osteogenesis Imperfecta

Ocular features are intensely blue sclera (due to visualization of the underlying choroid through a thin sclera) which remains blue throughout life, low ocular rigidity, low central corneal thickness (0.443 mm as compared to 0.522 mm in normal controls), posterior embryotoxon, keratoconus, megalocornea, hyperopia and optic nerve damage due to deformities or fractures of calvarial bones. Rare ocular findings include congenital glaucoma, cataracts, choroidal sclerosis, and subhyaloid hemorrhage. Spontaneous rupture of the globe is very rare. The perilimbal region is often whiter than the remaining sclera, resulting in the *Saturn's ring*. There is decreased diameter of collagen fibers and change in their cross-striation pattern. Type II osteogenesis imperfecta (OI) (congenita), the lethal congenital form with severe bony deformities present with dark blue sclera and shallow orbits. In types III and IV, the sclerae may be blue at birth, but the intensity of the color decreases so that by adolescence or early adulthood the sclerae appear normal.

Weill-Marchesani Syndrome

It is almost opposite phenotype to Marfan syndrome. It may be autosomal recessive (19p13.3-p13.2) or AD (FBN, 15q21, the gene for Marfan syndrome). Systemic features include short stature, brachycephaly, brachydactyly characterized by short, stubby fingers and toes, short stubby spade-like hands and feet, stiff joints and most patients have normal intelligence. Ectopia lentis, usually inferior occurs in 50% of cases during late childhood or early adult life. Microspherophakia is common. Lenticular diameter may be as small as 6.75 mm, and the sagittal diameter of the lens may be increased by 25%. Subluxation occurs anteriorly to cause pupil block glaucoma or occasionally lens may dislocate into the anterior chamber. Other ocular features include myopia, angle anomalies, asymmetrical axial lengths and presenile vitreous liquefaction.

SKIN DISORDERS

Albinism

Albinism is a genetic disorder of melanin synthesis in which either the eyes alone (ocular albinism) or the eyes, skin and hair (oculocutaneous albinism [OCA]) may be affected. *Tyrosinase negative OCA (complete albinism)* is an autosomal recessive disease with no melanin production (pale skin, white hair) throughout life. These patients do not tan at sunlight. Ocular features are poor visual acuity due to foveal hypoplasia, pendular horizontal nystagmus which increases in bright illumination and diminishes with age, diaphanous and translucent iris giving rise to a *pink-eye*, hypopigmented fundus with visible large choroidal vessels, increased proportion of crossing fibers at optic chiasm, high refractive errors, high astigmatism, positive angle kappa, squint, absence of stereopsis and predisposition to basal cell carcinoma and squamous cell carcinoma of skin. Systemic syndromes associated with OCA are *Chediak-Higashi syndrome* (autosomal recessive, 1q42) with leukocyte abnormalities resulting in recurrent pyogenic infections and lymphoreticular malignancies, causing death within second decade; and *Hermansky-Pudlak syndrome* (autosomal recessive lysosomal storage disease) with defective platelet aggregation resulting in early bruising, restrictive lung disease, granulomatous colitis, and renal failure.

Alkaptonuria

It is an autosomal recessive disorder characterized by accumulation of homogentisic acid in collagenous tissues such as cartilage and tendon (ochronosis) due to defect in homogentisic acid oxidase. Systemic features are dark urine, dark sweat stains, prostatic and renal stones, cardiovascular changes, skin pigmentation in areas with increased sweat follicles (axilla and anogenital region) and in thin skin, especially over cartilage of the ears, nose, extensor tendons of the hand, and costochondral junctions, spondyloarthropathy and arthropathy. Ocular features are bluish-grey or black generalized pigmentation of the sclera most prominent over rectus insertion, and pigment globules in peripheral cornea. Scleral pigmentation typically starts in third decade of life.

Piebaldism

It is an autosomal dominant disorder due to mutations in the cKIT proto-oncogene (4q11-q12) resulting in a failure of neural crest melanocyte precursors to properly migrate into ventral abdomen, forehead, eyebrows, chin, chest, abdomen, and extremities. Iris heterochromia has been associated with this condition.

Atopic Dermatitis/Eczema

It is chronic, relapsing, pruritic inflammatory skin condition associated with asthma and hay fever. Thickening, crusting and vertical fissuring of the lids is seen associated with staphylococcal blepharitis and madarosis. Other features are vernal conjunctivitis in children, punctal stenosis, weeping fissures at the lateral canthi, conjunctival papillae, symblepharon, entropion, trichiasis, punctate keratitis, corneal ulceration, vascularization, and opacification; shield like anterior subcapsular cataract which may mature rapidly, keratoconus and retinal detachment.

Ichthyosis

Ocular manifestations include corneal opacities, conjunctivitis, and keratitis. Keratitis, ichthyosis, and deafness *(KID) syndrome* and the *collodion baby syndrome* (ichthyosis presenting in the neonatal period) are rare variants.

Incontinentia Pigmenti (Bloch-Sulzberger Syndrome)

It is an X-linked dominant condition (mutation in NEMO gene on chromosome Xq28) that is lethal in utero for boys. Ocular features are unilateral or markedly asymmetrical, microphthalmos with retrolental mass of glial tissue simulating retinoblastoma or retinopathy of prematurity, abnormal vascular anastomoses with peripheral zones of decreased perfusion and preretinal fibrosis, vision loss due to retinal detachment, optic atrophy, neonatal macular infarct, and occipital lobe infarct; cataract, uveitis, and blue sclera. Other less common findings are nystagmus, strabismus, ptosis, pigmentation of the conjunctiva, corneal scarring, and absence of the anterior chamber, persistence of the hyaloid artery, and myopia.

Oculodermal Melanocytosis (Nevus of Ota)

It is characterized by unilateral (90%) increase in number, size and pigmentation of melanocytes in the sclera and uvea and may also involve ipsilateral periocular skin (usually in distribution of ophthalmic and maxillary nerve), orbit, meninges and soft palate. Other ocular features are elevated intraocular pressures (infantile glaucoma, ocular hypertension, open-angle glaucoma, and acute angle-closure glaucoma), and asymmetric cup disc ratio. There is an increased incidence of uveal, cutaneous, orbital, and intracranial melanoma, however the risk seems low.

Linear Nevus Sebaceum (Nevus of Jadassohn)

It usually occurs on the face and is associated with ocular malformations in approximately one half of cases including microphthalmia, choristomas especially conjunctival, and coloboma of the lids, iris, choroid, or optic nerve.

Multiple Endocrine Neoplasia Type 2B (MEN 2B, The Mucosal Neuroma Syndrome)

It is a hamartoneoplastic syndrome characterized by medullary thyroid carcinomas (MTC), pheochromocytomas, mucosal neuromas (tongue, lip), and ganglioneuromas of the intestinal tract, marfanoid habitus, and ophthalmic abnormalities. Ocular features are mucosal neuromas at eyelid margins, subconjunctival neuromas and medullated nerve fibers in the cornea.

Refsum Disease

It is an autosomal recessive condition due to deficiency in phytanic acid alpha-hydrolase resulting in accumulation of phytanic acid throughout the body. Infantile disease is characterized by dysmorphic facies, mental handicap, hepatomegaly and deafness. Adult disease presents with cerebellar ataxia, polyneuropathy, anosmia, deafness, cardiomyopathy and ichthyosis. Ocular features are retinitis pigmentosa, cataract, prominent corneal nerves, optic atrophy, nystagmus and poorly dilating pupils. Other systemic disorders associated with retinitis pigmentosa are *Bassen-Kornzweig syndrome (abetalipoproteinaemia)*, characterized by deficiency of fat soluble vitamins (Vitamin A, D, E, K) and acanthocytosis; *Kearns-Sayre syndrome* (chronic progressive external ophthalmoplegia with cardiac conduction defects), *Bardet-Biedl syndrome* (short stature, obesity, hypogaonadism, polydactyly, kidney disease), and *Usher syndrome* (deafness and vestibular dysfunction).

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a group of autosomal recessive conditions due to defective DNA repair after ultraviolet induced damage resulting in increased predisposition to various

skin malignancies. Ocular complications are photophobia, conjunctivitis, keratitis, even corneal perforation, dry eye, lid lesions with ectropion or entropion, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, conjunctival malignancies, and angiosarcoma of limbus.

Erythema Multiforme and Stevens-Johnson Syndrome

Ocular features in acute setting are hemorrhagic crusting of the lid margins, papillary conjunctivitis, conjunctival membranes and pseudomembranes, severe hyperemia, hemorrhages, blisters, patchy infarction and ulceration, corneal involvement from punctate erosions to larger epithelial defects, secondary bacterial keratitis and occasionally perforation. Late ocular feature is limbal stem cell deficiency with severe dry eye. There is keratinization of the conjunctiva and lid margin with or without abrasive plaque formation, irregular posterior lid margin, forniceal shortening and symblepharon formation, cicatricial entropion and ectropion, trichiasis, metaplastic lashes, ankyloblepharon, corneal scarring, vascularization and keratinization; fibrosis of the lacrimal puncta or lacrimal gland ductules and conjunctival metaplasia with loss of goblet cells.

NEUROCUTANEOUS SYNDROMES

Neurofibromatosis

Common ocular features are neurofibroma of lid either plexiform or nodular, causing mechanical ptosis, unilateral or bilateral optic pathway glioma (more like a hamartoma, with good prognosis) with clear cut margin due to intact dural sheath involving optic nerve and extending posteriorly to chiasm or hypothalamus, and Lisch nodules, which are elevated, smooth, clear to yellowish or brown, gelatinous, dome-shaped hamartomas of iris appearing in second to third decade and eventually present in 95% of all patients. Other features are orbital tumors like optic nerve neurilemmoma (Schwannoma), plexiform neurofibroma and meningioma; spheno-orbital encephalocele due to dysplasia or absence of the greater wing of the sphenoid bone resulting in a pulsating proptosis, without bruit or thrill, congenital ectropion uvae, mammillations of iris, prominent corneal nerves (nodular or myelinated or medullated), glaucoma associated with ipsilateral upper lid neurofibroma, or facial hemiatrophy or ectropion uvae; choroidal naevi which can turn malignant and retinal astrocytoma. Other findings are enlargement of the optic foramen, underdevelopment of the orbital bones, café-au-lait spots of lids, conjunctival nodular neurofibroma, thickened conjunctival nerves, nodular swelling of the ciliary nerves, posterior embryotoxon, unilateral keratoconus, buphthalmos, dense abnormal tissue in the chamber angle, defects of Schlemms canal, neurofibroma of the iris, iris neovascularization, anterior subcapsular cataract (rare), neurofibroma of the ciliary body, choroidal ganglioneuromas, diffuse neurofibroma of choroid, café-au-lait spots on the retina, sectoral retinal pigmentation, sectoral chorioretinal scar, myelinated/medullated nerve fibers, typical peripheral retinoschisis, congenital hypertrophy of the retinal pigmented epithelium (RPE), optic nerve drusen, hamartoma of the optic disc, primary optic atrophy due to tumor pressing over optic nerve, secondary atrophy due to papilledema, glioma of optic nerve head (rare), extraocular muscle palsy, and strabismus.

Neurofibromatosis Type 2 (Central Neurofibromatosis)

Common ocular features are cataracts (posterior subcapsular cataract, capsular, cortical or mixed) developing in third decade in two-thirds patients, features due to acoustic neuroma (decreased corneal sensation, facial palsy, Bruns nystagmus due to pressure on flocculus), ocular motility defect, epiretinal membrane, congenital hypertrophy of retinal pigment epithelium, astrocytic hamartomas, combined hamartoma of retinal pigment epithelium and retina, papilledema and secondary optic atrophy. Other features are optic nerve sheath meningioma, optic nerve glioma, unilateral Lisch nodules and an abnormal electroretinogram.

Tuberous Sclerosis Complex

Ocular involvement is in form of retinal or optic nerve astrocytic hamartoma (or phacoma) with tapioca grain or fish egg or mulberry appearance in 50% patients, and adenoma sebaceum of lids. Three types of retinal hamartoma has been described—(1) a more translucent, soft-appearing, relatively flat lesion usually located in the peripheral fundus; (2) an elevated, nodular, calcific mulberry lesion; and (3) intermediate type. The retinal lesions generally do not require treatment as they do not grow. The retinal tumors are generally sparsely vascularized or nonvascularized. Rarely visual loss occurs due to foveal involvement, continuing growth of nodular lesions, compression of visual pathway by tubers, and secondary optic atrophy following hydrocephalus. Rarely, vitreous seeding may be associated with vitritis and hemorrhage. Astrocytic hamartomas found in the retina or brain, are often calcified. Other ocular features are poliosis, angiofibroma of lid and conjunctiva, megalocornea, embryotoxon, progressive external ophthalmoplegia, sectoral pigmentation of iris with spots of hypopigmentation, atypical iris coloboma, and localized hypopigmented retinal lesion with ash leaf configuration.

von Hippel-Lindau Disease

Typical ocular finding is retinal or optic nerve head capillary hemangioma or hemangioblastoma, which may be endophytic or less commonly exophytic. 50% of patients with solitary hemangiomas and virtually all patients with multiple lesions have von Hippel-Lindau disease. The lesions are typically bright orange red, oval or round, elevated located at temporal retina with dilatation and tortuosity of the supplying artery and draining vein extending from the optic disc (feeder vessels). It may be complicated by hard exudates, macular edema or hole, epiretinal membrane, bleed, uveitis, exudative retinal detachment, fibrotic bands causing tractional or rhegmatogenous retinal detachment, vitreous hemorrhage, neovascular glaucoma, postpapilledema optic atrophy, and phthisis bulbi. In juxtapapillary lesions dilated vessels are less conspicuous. Exophytic tumors arise from the outer retina and occur most commonly in the peripapillary region. 25% of retinal angioma patients have CNS hemangiomas as well.

Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)

Glaucoma occurs in approximately 71% of patients and is more common when the cutaneous hemangioma involves the eyelid and when prominent conjunctival or episcleral hemangiomas are present. The early-onset glaucoma is due to trabeculodysgenesis with a flat, anterior iris insertion like primary infantile glaucoma. Later-onset glaucoma is due to elevated episcleral venous pressure, although anomalous angle structures may have a role. 40% of patients with Sturge-Weber syndrome (SWS) may have choroidal hemangioma, and 50% of all choroidal hemangiomas occur in SWS patients. Choroidal hemangiomas may be circumscribed, discrete, appearing as yellowish, elevated, circular areas, which disappear or decrease in visibility with scleral depression.

Wyburn-Mason Syndrome

Unilateral racemose hemangioma (arteriovenous malformation) is seen in the fundus characterized by dilated, bright red arteries

and veins which communicate without an intervening capillary bed. Similar lesions are present in ipsilateral midbrain, basofrontal region or the posterior fossa, which may spontaneously bleed or cause epilepsy.

Ataxia-Telangiectasia (Louis–Bar Syndrome)

Ocular features include conjunctival telangiectasia (bilateral dilated and corkscrew, bulbar conjunctival vessels at interpalpebral area) developing at age of 4–7 years, ocular motor apraxia with head thrusts and the inability to generate saccades and loss of optokinetic responses develop at a later age.

Klippel-Trenaunay Syndrome (KTS, Angio-osteohypertrophy)

It is a sporadic disease characterized by triad of cutaneous hemangiomata especially of an extremity, hemihypertrophy of bone and soft tissue of the affected limb, and varicosities. The eye ipsilateral to the affected limb is generally affected. Ocular features are orbital varices and retinal varicosities, glaucoma, cataracts, heterochromia, and Marcus-Gunn pupil.

ENDOCRINE METABOLIC DISORDERS

Cystinosis

Extensive ocular involvement is seen in form of progressive deposition of scintillating, iridescent cystine crystals in the cornea (keratocytes) by 1 year age with intense photophobia, blepharospasm, epithelial erosions and visual disability by the end of the 1st decade. Deposition of the corneal crystals begins in the anterior stroma and progress posteriorly, and starts from the periphery of the cornea to the center. Topical cysteamine 0.2% can reverse corneal crystal deposition. The crystal can get deposited in subepithelial tissues of conjunctiva; in sclera and episclera; in epithelium and stroma of iris; in pigmented and nonpigmented epithelium and connective tissue of ciliary body; in choroid, mainly within fibrocytes and histiocytes; in retinal pigment epithelium; in meninges and fibrovascular pial septae of the optic nerves; and in extraocular muscles. Retinal features like progressive pigmentary retinopathy, yellow mottling of the macula, glistening crystal-like deposits at retina may present before corneal involvement. Glaucoma is due to pupillary-block caused by thickening and rigidity of the iris due to crystal deposition, narrow anterior chamber in children, or primary open angle glaucoma in adults. Nephropathic late onset form is milder with less severe and late involvement of kidney and eye. In non-nephropathic or ocular or adult or benign form, only cornea is involved sparing retina and kidney.

Diabetes Mellitus

Common ocular features in diabetes are refractive changes (myopia with hyperglycemia and hypermetropia due to hypoglycemia due to change in refractive index of lens), photopsia and diplopia in cerebral hypoglycemia, decreased accommodation, pupil sparing third nerve palsy, painful ophthalmoplegia, xanthelasma and recurrent stye or internal hordeolum; telangiectasia, sludging of the blood in conjunctival vessels, subconjunctival hemorrhage, decreased corneal sensations (due to trigeminal neuropathy), punctate kerotapathy, higher incidence of infective corneal ulcers, delayed epithelial healing due to abnormality in epithelial basement membrane, wrinkling of Descemets membrane, hydrops of pigment epithelium of iris (due to transient glycogen storage), pigment release into anterior chamber (due to surgery, or after dilatation), rubeosis iridis, cataract, diabetic retinopathy and vitreous hemorrhage and fibrovascular proliferation in proliferative diabetic retinopathy, lipemia retinalis, increased incidence of primary open angle glaucoma (POAG), neovascular glaucoma, hypotony in diabetic ketoacidosis (due to increased plasma bicarbonate levels), diabetic papillopathy and ischemic optic neuropathy. Classic diabetic cataract consists of snowflake cortical opacities occurring in the young diabetic.

Both nonproliferative and proliferative type of diabetic retinopathy can be seen. Proliferative diabetic retinopathy is more common in type 1 diabetes. Nonproliferative diabetic retinopathy is characterized by microaneurysm, intraretinal hemorrhages (superficial or splinter hemorrhage and deep or dot blot hemorrhage), cotton wool spots (soft exudates) and hard exudates. Proliferative diabetic retinopathy is characterized by neovascularization of within one disc diameter of optic disc or in retina, vitreous hemorrhage, preretinal hemorrhage, tractional retinal detachment, combined tractional and rhegmatogenous retinal detachment, and neovascular glaucoma.

Galactosemia

Bilateral cataracts, with a central *oil droplet* opacity (due to accumulation of galactitol or dulcitol) appear within weeks of life. Other ocular features are nystagmus, strabismus, and vitreous hemorrhage, probably due to coagulopathy, retinal scarring and pigmentary changes.

Mucopolysaccharidoses

Ocular features are progressive corneal clouding, pigmentary retinal degeneration, optic atrophy, sometimes papilledema, and in some cases glaucoma. Corneal involvement is characterized by punctate corneal opacification and diffuse stromal haze. Other features are pigmentary retinopathy (not seen in Morquio or mucopolysaccharidoses [MPS] IV, Maroteaux-Lamy or MPS VI, and Sly or MPS VII), optic atrophy which is most severe in Hurler (MPS IH) and rare in Maroteaux–Lamy or MPS VI and Sly or MPS VII, and glaucoma in Maroteaux-Lamy or MPS VI (angle closure glaucoma) and Scheie (MPS IS).

Lowe Oculocerebrorenal Syndrome

It is a rare X-linked recessive disorder affecting the central nervous system, eyes, and kidneys. The diagnostic triad includes congenital cataracts, mental retardation, and renal tubular dysfunction. Other features are hypotonia and areflexia, proximal tubular acidosis, aminoaciduria, phosphaturia, frontal prominence, chubby cheeks, sunken eyes, failure to thrive and low-molecular-weight proteinuria. 50% cases have glaucoma. This syndrome is a cause of Fanconi syndrome. This syndrome is caused by mutations in the OCRL1 gene, encoding inositol polyphosphate-5-phosphatase. It is one of rare conditions in which congenital glaucoma and congenital cataract coexist.

Wilson Disease

It is an autosomal recessive disorder (chromosome ATP7B, 13q 14.3) of copper transport due to defective incorporation of copper into ceruloplasmin (abnormally low ceruloplasmin levels in blood) and biliary excretion of copper; though intestinal absorption of copper is normal. Systemic features are liver disease (icterus), basal ganglia dysfunction (abnormal movements) or psychiatric disturbances. Cornea is involved in nearly all patients and is characterized by a zone of copper granules in the peripheral part of Descemets membrane (Kayser-Fleischer ring, best detected on gonioscopy when subtle) starting near superior and inferior limbus which change color (golden to greenish yellow, bronze, or brownish) under different types of illumination and may disappear with penicillamine therapy. The Kayser-Fleischer ring is often absent in patients with acute liver disease and in asymptomatically affected siblings of patients with Wilsons disease.

Menkes Disease

It is an X-linked recessive (ATP7A gene, chromosome Xq21.1) disorder, with disturbance in the cellular transport of copper and defective intestinal absorption of copper, resulting in copper deficiency, and defective synthesis of copper enzymes. Ocular features are sunken eyes due to decreased orbital fat; pale, *steely*, stubby and sparse eyebrows; light blue or gray irides with a delicate stromal pattern, generalized hypopigmentation of the fundus with increased visibility of the choroidal pattern, tortuosity of the retinal arterioles, poorly defined macular landmarks, disc pallor evolving with time, nystagmus, strabismus, blepharitis, dacryostenosis, and possible tear deficiency.

Lipid Storage Disorders

They are usually autosomal recessive lysosomal storage disorders resulting in deposition of lipid in viscera, central nervous system and retina due to deficiency in certain enzymes involved in lipid metabolism. The typical fundus finding is cherry red spot, due to accumulation of lipids in the ganglion cell layer of the retina, giving the retina a white appearance. As ganglion cells are absent at the foveola, this area retains relative transparency and contrasts with the surrounding opaque retina, and choroidal vasculature is strikingly visible at fovea resulting in cherry red appearance. With time the ganglion cells die and the spot becomes less evident. The late stage of the disease is characterized by degeneration of the retinal nerve fiber layer and consecutive optic atrophy.

GM1 Gangliosidosis (Generalized)

Corneal clouding and macular cherry-red spot (in 50%).

Mucolipidosis Type I (Sialidosis)

Corneal clouding, macular cherry-red spot, optic atrophy and sometimes punctate lens opacities.

GM2 Gangliosidosis (Tay-Sachs Disease)

Macular cherry-red spot that is present by 3 months and optic atrophy after 1 year, with blindness by the age of 2 years.

Niemann-Pick Disease

Macular cherry-red spot in 50% and subtle corneal clouding. Type C (chronic neuropathic) may present with gaze palsy and abnormal eye movements but cherry red spot is not seen.

Farber Disease

Macular cherry-red spot, pingueculum-like conjunctival lesions and nodular corneal opacity.

Gaucher Disease

Type I, has ocular features including white deposits in anterior chamber structures (the corneal endothelium, pupillary margin, the angle, and ciliary body), prominent pingueculae, grayish perimacular retina with some white spots, pigmentary changes in the macula, macular atrophy, abnormally permeable retinal vasculature, rarely corneal opacity and uveitis. Oculomotor apraxia, supranuclear horizontal gaze palsy and abnormal optokinetic responses are common in types II and III. Type II may present with paralytic strabismus.

Thyroid Eye Disease

Pediatric Graves' disease is an uncommon condition. Ocular findings are often independent of the degree of thyrotoxicosis and may appear before the onset of hyperthyroidism. Lid lag, soft tissue involvement and proptosis are the commonly seen, but restricted eye muscle motility; severe strabismus and optic neuropathy are usually not seen.

HEMATOLOGIC DISORDERS

Leukemia

Ocular features are venous dilatation, tortuosity and irregularity; intraretinal, preretinal and vitreous hemorrhages, cotton wool spots and retinal hemorrhages with white centers (Roth spots), optic nerve infiltration, orbital involvement, iris thickening, iritis, pseudohypopyon, spontaneous subconjunctival hemorrhage and hyphema, periorbital ecchymosis, and cranial nerve palsies. Myeloid sarcoma (granulocytic sarcoma) is caused by malignant cells of myeloid origin with characteristic green color (chloroma). Orbital involvement usually presents at about age 7 years with rapid onset of proptosis, sometimes bilateral, which may be associated with ecchymosis and lid edema. Chronic leukemia is characterized by microaneurysms, retinal venous occlusions, peripheral retinal neovascularization, and choroidal infiltrates giving rise to leopard skin appearance.

Anemia and Thrombocytopenia

Ocular features are retinal venous tortuosity which may be related to the severity of anemia, especially in beta-thalassemia major; dot/blot and flame-shaped hemorrhages, cotton wool spots and Roth spots which are unassociated with duration and type of anemia and seen with thrombocytopenia in aplastic anemia; and optic neuropathy with centrocecal scotomas in pernicious anemia.

Hyperviscosity Syndrome

This is a group of diseases characterized by increased blood viscosity due to polycythemia or to abnormal plasma proteins (e.g., Waldenström macroglobulinemia). Ocular features are retinal hemorrhages and venous dilatation, retinal vein occlusion and conjunctival telangiectasia.

Sickle Cell Retinopathy

Sickle cell retinopathy can be proliferative or nonproliferative. Proliferative retinopathy is seen in 33% of SC, 14% of ST and 3% of SS patients. It is characterized by peripheral arteriolar occlusion and ischemia, peripheral arteriovenous anastomoses, *sea-fan* neovascularization of which 30–40% of undergo autoinfarction, vitreous hemorrhage, extensive fibrovascular proliferation and retinal detachment. Nonproliferative retinopathy is characterized by venous tortuosity, *silver-wiring* of arterioles in the peripheral retina; pink, preretinal or superficial intraretinal hemorrhages at the equator (Salmon patches), *black sunbursts* (patches of peripheral retinal pigment epithelium [RPE] hyperplasia), macular depression sign due to foveal atrophy, peripheral retinal holes, macular arteriolar occlusion in 30% of patients, choroidal vascular occlusion in children, and less commonly acute CRAO, retinal vein occlusion, and angioid streaks. Other features are comma or cork screw shaped vascular conjunctival lesions, circumscribed areas of ischemic iris atrophy, and rubeosis iridis.

Langerhan Cell Histiocytosis

Ocular features are unilateral or bilateral osteolytic orbital lesions and soft tissue involvement typically in the superotemporal quadrant resulting in proptosis, strabismus due to extraocular muscle involvement, and vision loss due to optic nerve involvement.

NEUROLOGICAL DISORDERS

Aicardi Syndrome

It is a triad consisting of wide spread round or oval chorioretinal lacunae clustered around disc, infantile spasms and agenesis of corpus callosum. Other ocular features are hypoplastic, colobomatous or pigmented optic nerve head, microphthalmos, iris colobomas, persistent pupillary membranes and cataract.

Arnold-Chiari Malformation

Ocular features are papilledema, downbeat nystagmus, ataxia, multiple cranial neuropathies, and corneal anesthesia with painless scarring of the cornea (due to stretching of the trigeminal nerve).

Acquired Myasthenia Gravis

Ocular manifestations include a variable ptosis and strabismus that is worse in the evening or on fatigue.

Batten Disease (Juvenile Neuronal Ceroid Lipofuscinosis)

It is an autosomal recessive disease due to deletion in the CLN3 gene (chromosome 16p) in juvenile form. Ocular features are subtle pigmentary changes at macula, bull's eye maculopathy, nyctalopia, retinitis pigmentosa (retinal arterial narrowing, optic atrophy, and pigment disturbances within the fundus).

Mitochondrial Abnormalities

Mitochondrial abnormalities with ocular involvement include chronic progressive external ophthalmoplegia, MELAS syndrome (myopathy, encephalopathy, lactic acidosis, and stroke), MERRF syndrome (myoclonus, epilepsy, and ragged red fibers), and Leber hereditary optic neuropathy. *Kearns-Sayre syndrome* is a mitochondrial cytopathy characterized by triad of chronic progressive external ophthalmoplegia, retinitis pigmentosa, and cardiac conduction defects (heart block).

Neuroblastoma

Orbital metastases may be bilateral and typically present with an abrupt onset of proptosis accompanied by a superior orbital mass and periorbital ecchymosis.

Opsoclonus myoclonus syndrome (Opsoclonus myoclonus ataxia) is an autoimmune disorder characterized by 'dancing eyes', seen classically in neuroblastoma as a paraneoplastic manifestation, and rarely in celiac disease.

Multiple Sclerosis

Ocular features are optic neuritis (usually retrobulbar), internuclear ophthalmoplegia, nystagmus, skew deviation, ocular motor nerve palsies, hemianopia, intermediate uveitis and retinal periphlebitis.

RHEUMATOLOGIC DISORDERS

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common disease associated with childhood anterior uveitis, females are commonly involved. Iridocyclitis is associated most commonly with the pauciarticular onset form of JIA. Typical ocular features are bilateral (70%), nongranulomatous chronic anterior uveitis, posterior synechia, posterior subcapsular cataract, band shaped keratopathy, strabismus, and even atrophic bulbi. It is very

important to regularly screen children at risk for at least 7 years from the onset of arthritis or until the age of 12 years. Regular slit lamp examination should be done as follow: Systemic onset = not required; Polyarticular onset = every 9 months; Polyarticular onset + antinuclear antibody (ANA) = every 6 months; Pauciarticular onset = every 3 months; Pauciarticular onset + ANA = every 2 months.

Behçet Syndrome (Adamantiades-Behçet Disease)

It consists of triple symptom complex of recurrent aphthous oral ulcers, genital ulcers and uveitis. Other systemic manifestations are erythema nodosum, arthritis, and meningoencephalitis. The uveitis is classically bilateral in 80% cases, nongranulomatous with hypopyon. Posterior segment manifestations may be occlusive retinal vasculitis with surrounding intraretinal hemorrhage and retinal edema, severe vitritis, and disc edema. Progressive damage to the sensory retina results in marked attenuation of the arterioles.

Kawasaki Disease

Ocular manifestations are bilateral nonpurulent bulbar conjunctivitis, mild and self-limited anterior uveitis, superficial punctate keratitis, vitreous opacity, papilledema, orbital myositis, and extraocular muscle palsy, and as a late sequel dacryocystitis.

Sjögren Syndrome

It consists of a triad of symptoms including dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and rheumatoid arthritis. Dry eye is due to deficiency of aqueous layer of tear film. Rarely Adie pupil has been reported.

Systemic Lupus Erythematosus

Ocular manifestations of lupus include large amorphous cotton-wool spots, which correlates well with the activity of the systemic illness, madarosis, dry eye, eyelid lesions, scleritis, peripheral ulcerative keratitis, retinal arterial occlusion, retinal vasculitis, and optic neuritis.

GASTROINTESTINAL DISORDERS

Alagille Syndrome

Posterior embryotoxon or prominent and anteriorly displaced Schwalbe line in 95% of cases, retinal pigmentary changes in one-third patients and optic disc drusen.

Ulcerative Colitis

Acute anterior uveitis is seen in about 5% of patients.

Crohn's Disease

Ocular features include acute anterior uveitis in 3% patients, nodular scleritis (more common than ulcerative colitis), diffuse and nodular episcleritis, rarely chorioretinitis, vasculitis, and papillitis.

RENAL SYSTEM

Alport Syndrome

It is an oculorenal syndrome characterized by ocular anomalies, progressive sensorineural hearing loss, and hemorrhagic nephropathy. Pathognomonic manifestation is anterior lenticonus, which is bilateral in 75% cases. Other ocular manifestations are dot-and-fleck retinopathy, posterior polymorphous corneal dystrophy, and recurrent corneal erosion.

Hypertension

Hypertensive retinopathy has been classified by Keith Wagner Barker, Schie, and Wong and Mitchel. Signs of hypertensive retinopathy are arteriolar narrowing which may be focal or generalized, cotton wool spots, flame-shaped retinal hemorrhages, retinal edema, and macular star configuration in chronic retinal edema due to deposition of hard exudates around the fovea in the layer of Henle, optic disc edema. Features of arteriolosclerosis are broadening of arteriolar light reflex, deflection of veins at arteriovenous crossings (Salus sign), *Copper-wiring* of arterioles, banking of veins distal to arteriovenous crossings (Bonnet sign), tapering of veins on both sides of the crossings (Gunn sign), right-angled deflection of veins, and *Silver-wiring* of arterioles. Other ocular features are Elschnig spot (focal choroidal infarct), Siegrist streak (fleck of fibrinoid necrosis along choroidal vessels), and exudative retinal detachment. Hypertension has been associated with subconjunctival hemorrhage, retinal venous occlusion, retinal artery macroaneurysm, age related macular degeneration, suprachoroidal hemorrhage, and anterior ischemic optic neuropathy.

MORE ON THIS TOPIC

Kanski JJ, Bowling B, Ken K. Clinical ophthalmology: a systematic approach. New York: Elsevier/Saunders, Edinburgh; 2011.

Wright KW, Spiegel PH, Thompson LS. Handbook of Pediatric Eye and Systemic Disease. USA: Springer; 2006.

Chapter 47.13
Visually Impaired Child
Kirti Singh, Ankush Mutreja

The importance of providing care for children with low vision is recognized by many initiatives, such as Vision 2020, Oslo Workshop on Low Vision 2004, and United Nation's Global campaign, Education for All. Majority of children with low vision have functional vision which if properly utilized and maximized, can result in independent and productive life. However, such children are rarely encouraged to develop the use of this residual vision. Often existence of such vision is ignored resulting in these children being treated at par with blind peers. Children with low vision are placed in a difficult position in social and educational front, as they are not blind enough to be entitled to rehabilitation and social services, but not sighted enough to live a life with normal visual functions and compete with their sighted peers. Efficient use of low vision through an instructional program is thus the need of the hour.

DEFINITION

In 1992, World Health Organization (WHO) published a working definition of low vision as "is one who has impairment of visual functioning even after treatment and/or standard refractive correction, and has visual acuity of less than 6/18 to light perception, or a visual field of less than 10 degrees from the point of fixation, but who uses, or is potentially able to use, vision for the planning and/or execution of a task for which vision is essential." International Classification of Diseases, 9th revision defines it as corrected visual acuity of less than 6/18 to perception of light, in the better eye. Treatable conditions are refractive errors, cataract, and posterior capsular opacification postcataract surgery; all other causes including amblyopia are considered untreatable.

Functional low vision in children is characterized by irreversible visual loss, reduced ability to perform many daily activities, like recognizing people in the street, reading blackboards, writing at same speed as peers, and playing with friends. Low vision thus maybe defined as *"vision that, when corrected by optimal refractive correction, is not adequate for the patient's needs."* Vision is an organizing sense that allows perception of distant objects and to make connections between them. Decreased mobility results in distorted and limited information about the physical world, which in turn gives rise to inaccurate or missed concepts about people and objects. Lack of complete feedback from the world further delays entry of these children into the social fabric of society and family. Education is affected most, as 80% of education inputs are through visual sense. Thus visual impairment translates into impaired education, delay in psychomotor/cognitive skills, language acquisition and personality development.

EPIDEMIOLOGY

Prevalence of blindness in developed economies like Western Europe, USA, Australia, New Zealand and Japan is 0.3%, in Latin America, China and Middle East it is 0.5–0.7%, in Asia 1.0% and in sub-Saharan Africa the figure is 1.4%. Global estimate of blindness is 45 million, with a further 135 million individuals classified as having low vision. Distribution of blindness according to age is associated with essentially untreatable degenerative processes due to aging in the developed world whereas in the developing world higher proportion is due to childhood blindness. Of the 1.5 million blind children worldwide, 1.3 million reside in Asia and Africa, and 75% of this blindness is both preventable and/or curable. Approximately 5 million children worldwide have low vision. No estimates on blindness/low vision are available for Indian children.

ETIOLOGY

The WHO classifies childhood blindness according to anatomical site most affected and underlying etiology **(Box 1)**. Genetic causes account for majority of childhood visual impairment in developed world, whereas in developing world infections rule the list. Common global causes of low vision in young are retinitis pigmentosa, hereditary macular degeneration, cataract, optic atrophy and glaucoma. In the Indian context, corneal opacity is most common cause of corneal blindness, due to precipitation of vitamin A deficiency subsequent to measles or debilitation. Distressingly, between 60% and 80% of children die within 2 years of becoming blind.

EVALUATION OF CHILDREN WITH LOW VISION

Children with low vision can attain a quality of life better than their caregivers' expectation provided their treatment follows the following algorithm.
1. Establishing cause of visual loss.
2. Appropriate surgical intervention where feasible.
3. Visual function assessment (distance/near vision, contrast sensitivity, visual field).
4. Accurate refraction and provision of spectacles.
5. Assessing and prescribing low vision devices.
6. Assessment for need of nonvisual aids.
7. Educational support and training for low vision rehabilitation.

Clinical History

Details of birth history, ocular issues in other siblings, consanguinity and antenatal issues including maternal nutrition, vaccination status and morbidity are to be noted. The emotional state of child, parents has to be evaluated in addition to socioeconomic strata. This determines acceptability of low visual aids (LVA) and sets objectives for the program. Simple observation of child like his ability to navigate in examination room, body language, eccentric head posture provides clues about visual status. Psychological assessment motor behavior, language and cognitive adaptive skills also need to be assessed.

Visual Acuity

This gives a baseline estimate of vision and allows disease monitoring (progression or stability). Snellen chart has many shortcomings for low vision examination including insufficient optotypes, large gaps in target size interval and variable contrast.

BOX 1 Common causes of childhood blindness

- *Prenatal causes*: (time of conception or during intrauterine period):
  - *Congenital anomalies*: Anophthalmia, microphthalmia, coloboma
  - *Congenital cataract/glaucoma*
  - Corneal and *retinal dystrophies*
- *Perinatal causes*: (28th week of gestation to 1–4 weeks postbirth)
  - Cortical impairment from birth asphyxia
  - Ophthalmia neonatorum
  - Retinopathy of prematurity (ROP)
- *Postnatal causes*: Infections, xerophthalmia, keratomalacia, trauma, high refractive error
- *Prematurity*: ROP and cortical visual dysfunction.

Standardized charts like Bailey-Lovie Chart and early treatment of diabetic retinopathy study (ETDRS) chart measure distance vision more reliably. Special charts for use in patients with low vision like Feinbloom/Leas chart are also available **(Figs 1 and 2)**.

Visual acuity should be recorded *without correction, with best correction and with correction used by the child.* In addition to distance vision, near visual acuity must be assessed. This is important as the child's world consists of proximate objects like toys and mother in infancy, games in toddler age, and textbook reading in school age. Near visual acuity is measured with M notation for low vision patients and reading distance recorded. Monocular and binocular acuity assessment is done in varying illumination to simulate real life situations.

Refraction

Refraction by retinoscopy has to be performed under cycloplegia with 1% atropine for children less than 5 years, 2% homatropine /1% cyclopentolate for older children. Refer to chapter 47.3 on refractive errors for details. Contrast sensitivity, color vision and visual field (wherever possible) has to be assessed along with detailed ophthalmic examination including slit lamp **(Figs 3A and B)** and fundus evaluation.

Refractive Correction

This is prescribed in form of spectacles or contact lenses in uniocular aphakia.

Prescribing spectacles/Low vision aids The first option and aid tried is aspheric high power spectacles. Magnification requirement for *distance* is calculated by Kestenbaum formula which is inverse of measured distance visual acuity. For example, if best corrected distance visual acuity in better eye is 6/36, then required magnification for distance is 36/6 = 6X.

Required magnification for *near tasks* is calculated as: Equivalent viewing power (EVP) = Target Visual Acuity. This is equal to

$$= \frac{\text{Best corrected visual acuity}}{\text{Target visual acuity}} \times \frac{100}{\text{Working distance in cm}}$$

Example—Near vision recorded is N36. Target visual acuity required to enable child read print of textbook at a distance of 30 cm is N10 (default text size for standard books). Calculated EVP = (36/10) × (100/30) = 12D. The magnification of LVA device is obtained by dividing D by 4, which would be 12 ÷ 4 resulting in value of 3X.
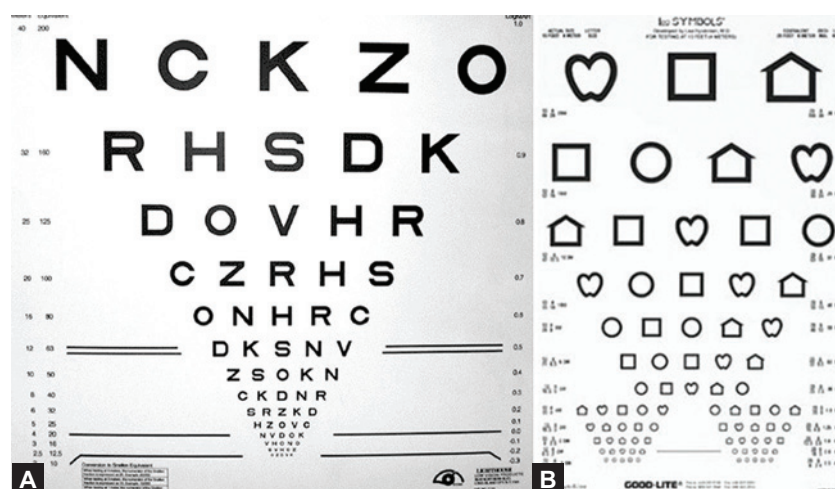
Figures 1A and B Logarithm of the minimum angle of resolution (LogMAR) and Lea chart *3 m* for *distance* vision. (A) The chart with alphabets; (B) Leas chart with figures for younger child

Figure 2 Lea near vision symbol chart and technique of using it for a child
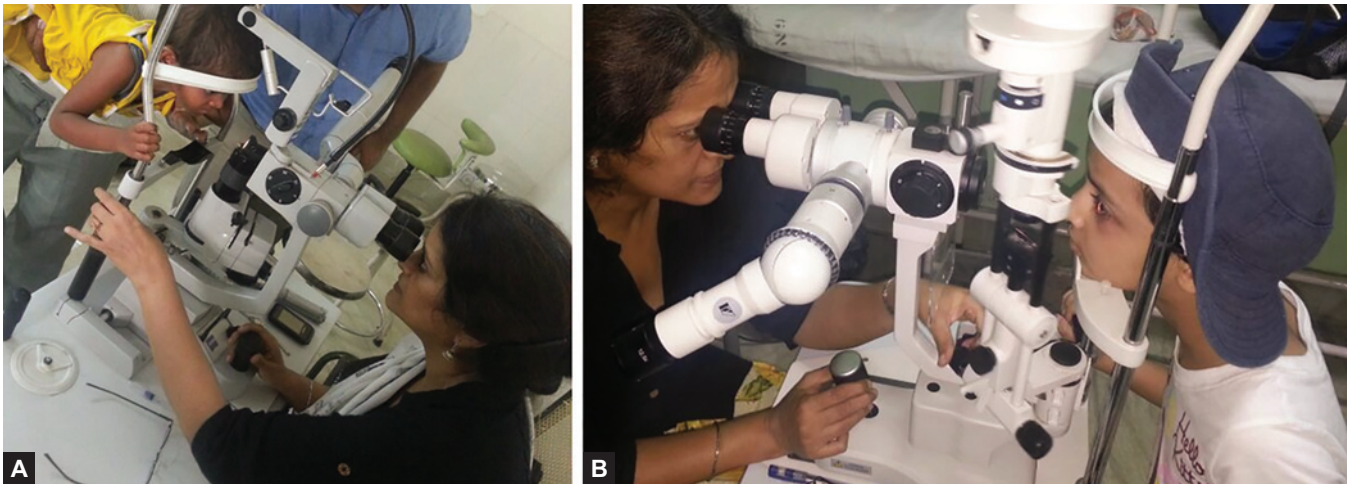
Figures 3A and B Technique for assessing a very young child on a regular slit lamp, in absence of a hand held slit lamp. (A) Euphemistically called the *helicopter position*; (B) Conventional examination for an older child

This near vision required magnification calculation is most relevant as most LVAs target near vision which is as it should be, since a child's world is in dealing with proximate things **(Figs 4A and B)**. If aspheric glasses are not effective or feasible then other LVAs and nonoptical devices detailed later, are tried as and where needed.

Education and Counseling

Prescription of LVA and training in their use is given after assessing visual needs, motivation, dexterity and ability to handle the aids. Limitations of LVA should be carefully explained, e.g., limited field with aspheric glasses necessitating bringing of the book very close, or a need for inclined reading stand.

LOW VISION AIDS

Early intervention with LVA strengthens visual abilities, reduces visual deprivation at an early age, provides accurate visual information, improves ability to learn and chances of receiving education in mainstream schools with sighted peers. In addition, learning to use low vision devices at an early age helps children to become confident with their use: it also allows them to feel

less socially awkward as they grow up and continue to use these devices. Thus it is important for the pediatrician to timely diagnose these children and refer in preschool age group. Enhancement of visual functions can be done by combination of environmental modifications **(Box 2)** and low vision devices. The three categories of LVA are (1) optical, (2) nonoptical, and (3) electronic devices.

Optical Low Vision Aids

Most children improve their near vision by employing their strong ability to focus on nearby objects (accommodation), or by *squinting* to produce a pinhole effect. An additional method to

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BOX 2 Environmental modifications for those with low vision

- Placing children near windows to give them better light when reading
- Allowing use of felt-tipped pens to produce thicker lines making it easier to read
- Using large print books
- Encouraging children to wear caps to prevent glare (e.g., patients with aniridia)
- Indoor environment modification, e.g., bold letters for signages, dark strips on stairs to avoid tripping, bold colored clocks

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Figures 4A and B Child with aspheric hypermetropic correction in right eye, left eye is occluded and child motivated to play with colored toys as part of amblyopia therapy

increase acquired magnification is by *approach method*, whereby children move their eyes closer to object of interest to see it in more detail. This creates *relative distance magnification*.

Optical LVA for Near Vision Tasks

Single vision spectacle magnifiers Children favor use of single-vision spectacle magnifiers, because they do not mind close working distances needed and have short and flexible limbs. Spectacles provide a large field of view, relax eye-strain and prolong viewing time. In addition it is hands-free. However a relatively short viewing distance is required with its use, causing head and neck fatigue after prolonged use.

Hand-held magnifiers These easy to handle magnifiers have flexible magnification **(Figs 5 and 6)**. Children can change either distance between magnifier and object/text, or distance between eye and magnifier. Greater distance between magnifier and object/text, translates into higher magnification. Decreasing distance between eye and magnifier also increases magnification power. Depending on text size, the child chooses most comfortable viewing distance. Availability of strong magnification powers, built-in illumination benefits children requiring above-average illumination, e.g., retinitis pigmentosa, maculopathy. However, use of hand-held magnifiers requires steady hands and good eye hand coordination, especially for high power lenses. This limits the usefulness of these devices for young children and those with upper limb disabilities.

Stand magnifiers These offer most stable image compared to single-vision spectacle magnifiers and hand-held magnifiers. These easy to manipulate magnifiers are a good choice for beginners, especially those requiring high magnification. The stand magnifier rests on surface of the reading material and thus provides stable image **(Figs 5 and 6)**. Movements with magnifiers are to be made in only two dimensions. Built-in illumination, provided by relatively bulky battery handle, is also available. The expense, bulk and requirement of a smooth surface for resting the stand are its drawbacks.

Dome magnifiers Type of specially designed stand magnifier which doubles magnification for those using relative distance magnification. Both single-vision stand and hand-held magnifier stand are easy to use **(Figs 5 and 6)**.

Optical LVA for Distance Vision Tasks

*Extra-short focus monocular telescope **(Figs 7A and B)*** This brings image of distant object many times closer and hence clearly visible.

A 4X telescope decreases distance of an object 20 m away to be visible at 5 m, and an 8X telescope shortens it to 2.5 m. It is useful for certain daily activities like reading blackboard, street signs and bus numbers. Use of this device requires intensive training to learn the focus control and target searching techniques. In addition, good eye-hand coordination to track targets especially moving ones is also required. Copying work from blackboard is strenuous as line by line has to be scanned with the telescope which by nature has a very limited field. A better option would be copying from a sighted peer's book. This is a benefit in integrated schooling explained later on in this chapter.

Nonoptical Devices

These extremely important ancillary aids to LVA are not stand alone. They involve environment modification to maximize use
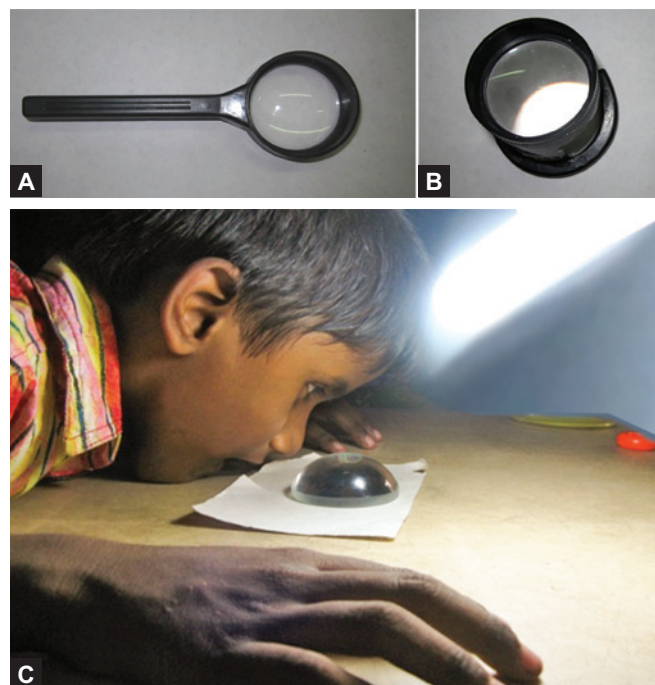
Figures 6A to C (A) Hand magnifier; (B) Stand magnifier; (C) A child using a dome magnifier. Note the table lamp to enhance illumination with light focuses on reading text
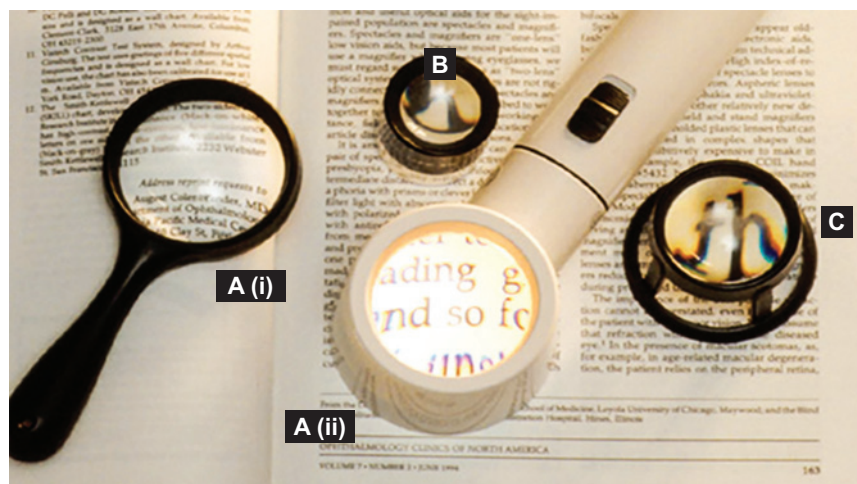
Figures 5A to C Magnifiers—(A) Hand-held magnifiers—illuminated (ii) and nonilluminated (i); (B) Stand magnifier; (C) Dome magnifier

Figures 7A and B (A) Use of a spectacle mounted telescope by a child. Telescope by nature of its reduced field can be only used monocularly for reading; (B) Hand-held telescope being used by a child to read the blackboard
Source: Dr Ilango, Aravind Eye Centre.

Figure 8 Reading stand with adjustable tilt and goose neck table lamp for focused illumination

Figure 9 Typoscope/reading or writing guide. Very useful for child using magnifier whose limited field of vision makes text followability difficult. Typoscope by separating lines ensures easy followability in reading text

of natural or artificial light, enhance contrast and detract from the problems inherent with optical LVA. For example, using any near task LVA requires the object to be held very close to the magnifying device. This requires short viewing distances and after few minutes the unnatural bending of body and neck over the table causes discomfort and abandonment of the reading activity. A simple modification of the table to have an adjustable tilt, helps to relieve this poor posture by reducing the short viewing distances and negating neck flexion.

Maximizing Illumination
- Table lamp with an elongated *gooseneck* directs and controls direction of light to the reading spot. This helps children who need above-average illumination **(Fig. 8)**.
- *Filters* Children with media opacities such as corneal scarring are sensitive to glare. For them special absorptive filters, preferably with side shields are useful for filtering scattered and glare-producing light. Simple devices like peaked caps with affront shade and hats are extremely useful for outdoor activities and navigation.

These nonoptical devices easily available at stationer, furniture, or optical shops.

Using Contrast
*Typoscope—Reading devices/slits **(Fig. 9)*** These simple devices assist children with writing or drawing and can be made by parent, teacher or clinician. It is made by cutting black card board into frames or windows to create reading slits or writing and drawing guides. Another way to assist reading is by drawing bold black lines on white paper, to make writing easier. Bold felt pens also help.

Electronic Low Vision Devices
A boon for the low vision child these devices are rapidly replacing the optical devices. They provide largest field of view, most comfortable viewing distances and highest magnification. However, they are the most expensive. Most commonly used electronic low vision device is closed-circuit television (CCTV) **(Fig. 10A)**. It offers brightness and contrast enhancement controls and is a good choice for children with severe visual impairment. Due to their size and weight they need to be fixed in one place. Portable electronic devices are currently less easily available and are very expensive. The latter comprise of a digital camera which captures images and enlarges them to the desired magnification.

The rapid advancement in mobile phones technology, especially the surge of smart phones **(Fig. 10B)**; a number of applications are available for the visually impaired to ease their lives and reduce their handicap. These applications help them in performing activities like choosing clothes, recognizing currency notes, recognizing people around them, etc., which are normal

Figures 10A and B (A) Indigenous close circuit television with reading text being magnified on screen;
(B) Use of smart phone to magnify print on a medicine bottle
Source: Dr Ilango, Aravind Eye Centre.

chores for the visually normal people but a mammoth task for the visually impaired.

REHABILITATION

Most causes of blindness and low vision are preventable or nonprogressive, so screening of preschool and school children is important to diagnose and manage any ocular pathology leading to visual impairment. Early screening and detection would also ensure early vision rehabilitation programs and thereby minimize impact of visual impairment. Visual impairment in general, affects four main functional areas: (1) orientation/mobility, (2) communication, (3) activities of daily life (ADL), and (4) sustained near vision tasks like reading and writing, including color vision. The effect on these four main areas varies depending on the type of impairment, its degree and other additional impairments. The pediatrician and ophthalmologist by forming a team could timely diagnose these children and subsequently decide about treatment modalities.

At toddler level, restoration of visual clues are crucial for overall development of the child and at preschool level decision as to mode and medium of education need to be decided. Children being more adaptable and adjusting than adults accept low vision devices rapidly. To maximize efficacy of LVA early prescription and training is the keystone. Good communication with parents and teachers would do a long way in easing out obstacles about use of LVAs. Parents and teachers should be encouraged to note any difficulties children may have when using their low vision devices, especially during the first home trial. They should also listen to any complaints children might make.

Schooling

Integrated Education

It is a system which imparts primary level education to children with mild to moderate disability with sighted peers so that the child has equal opportunities for learning and is able to interact with seeing children. Such schools help in a personality development of the low vision child and in addition help in changing stereotyped response of sighted people to poor vision. One of the major initiatives of Government of India to promote *integrated education* is the program of Integrated Education of Disabled Children (IEDC). In 1974, Ministry of Welfare, Central Government of India, initiated IEDC program to promote integration of students with mild to moderate disabilities into regular schools. Under this program children are provided with financial support for books, stationery, school uniforms, transportation, special equipment and aids to be retained in regular schools. According to recent estimates, IEDC is being implemented in 26 States and Union Territories, serving more than 53,000 students enrolled in 14,905 schools (Ministry of Information and Broadcasting, 2000).

Inclusion

It is an approach to educating students with special educational needs, where these children spend most or all of their time with nondisabled students. It differs from *integration* and *mainstreaming*, which were concerned with disability and *special educational needs* and implied learners changing or becoming *ready for* or deserving of accommodation by the mainstream. Inclusion is about the child's right to participate and school's duty to accept. Inclusion has two sub-types: (1) regular inclusion or partial inclusion, and (2) full inclusion.

Partial inclusion It implies special need children being educated in regular classes for minimum half of the day. Whenever possible with additional help or special instruction the student is treated like a full member of the general classroom. Specialized services are provided outside a regular classroom, particularly those requiring special equipment or might be disruptive to rest of the class (speech therapy), and students are pulled out of regular classroom for these services.

Full inclusion It implies students with special needs being educated with students without special needs, with appropriate supports and services.

MORE ON THIS TOPIC

Cox RFA, Reimer MA, Verezen CA, et al. Young children's use of a visual aid: an experimental study of the effectiveness of training. Dev Med Child Neurol. 2009;51:460-7.

Dale N, Salt A. Early support developmental journal for children with visual impairment: The case for a new developmental framework for early intervention. Child Care Health Dev. 2007;33:684-90.

Dandona L, Dandona R. Revision of visual impairment definitions in the International Statistical Classification of Diseases. BMC Medicine. 2006;4:7.

Dandona R, Dandona L. Review of findings of the Andhra Pradesh Eye Disease Study: policy implications for eye-care services. Indian J Ophthalmol. 2001;49:215-34.

Day S. Normal and abnormal visual development. In: David T. Pediatric Ophthalmology. Oxford UK: Blackwell Science; 1997. pp. 13-28.

Gilbert C. Blindness in children. BMJ. 2003;327:760-1.

Gilbert CE, Ellwein LB. RESC Study Group. Prevalence and causes of functional low vision in school-age children: results from standardized population surveys in Asia, Africa, and Latin America. Invest Ophthalmol Vis Sci. 2008;49:877-81.

Gogate P, Gilbert C, Zin A. Severe visual impairment and blindness in infants; cause and opportunities for control. Middle East Afr J Ophthalmol. 2011;18:109-14.

Labib TA, Sada MAE, Mohamed B, et al. Assessment and management of children with visual impairment. Middle East Afr J Ophthalmol. 2009;16:64-8.

Resnikoff S, Pascolini D, Mariotti SP, Pokharel GP. Global Magnitude of visual impairment caused by uncorrected refractive errors in 2004. Bull World Health Organ. 2008;86:63-70.

World Health Organization. The management of low vision in children. Report of a WHO Consultation: Bangkok, July 1992. Geneva: World Health Organization; 1993.

Section 48 COMMON SKIN PROBLEMS

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Chapter 48.1

Skin of the Newborn: Physiological and Pathological Changes

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During the neonatal period, the anatomical and physiological maturation of the skin is still in progress. Neonatal skin differs from that of children and adults with respect to both structural integrity as well as functional capacity. The neonatal skin, in general, is thinner with fewer intercellular adhesions, has fewer melanosomes, hair follicles and lesser eccrine secretions. **Table 1** outlines the structural development of the skin at neonatal stage with the corresponding functional attributes and their clinical significance. In preterm neonates, these attributes are further accentuated.

PHYSIOLOGICAL SKIN CHANGES

Majority of the physiological skin changes seen during neonatal period are attributable to the structural and functional immaturity of the skin and/or immaturity of the internal adaptive mechanisms that render the neonates respond differently to the external environmental factors. Hence, such cutaneous changes are essentially transient and resolve completely without treatment. Also, some of the maternal hormones that enter fetal circulation may produce transient skin changes in their newborns as described below.

Appearance of neonatal skin At birth, the skin of the *term neonate* is covered with vernix caseosa, a white gelatinous material that imparts an alkaline pH to the skin. It is believed to have many roles in the intrauterine development as well as protective effect on the maturing newborn skin against environmental factors. The vernix flakes off within a few hours of birth and the skin pH gradually declines to reach the normal acidic values by 4th week. The newborn skin may be covered with fine, short and minimally pigmented lanugo hairs especially on the back, forehead and shoulders. The skin of *preterm neonates* appears rather translucent

Table 1 Structural and functional status of neonatal skin and their clinical significance

Skin parameter	Development in neonates	Functional aspects	Clinical significance
Epidermal thickness	Completely developed	Although the epidermal thickness is similar to that of adults, systemic absorption of topically applied substances is increased due to greater surface area to body mass ratio, presence of occlusive conditions such as waterproof nappies, and high ambient temperatures and/or humidity	Increased risk of systemic toxicity from topically applied agents
Intercellular adhesions	Near complete in term but fewer in preterm neonates	Less efficient epidermal barrier function	Increased skin fragility, increased tendency to blistering and increased TEWL
Dermal thickness and subcutaneous fat	Fewer collagen and elastic fibers. Less subcutaneous fat	Increased heat loss	Increased risk of hyperthermia, particularly in preterm neonates in whom the autonomic thermoregulatory mechanisms are also underdeveloped
Melanosomes	Fewer in term and much lesser in preterm neonates	Decreased natural protection from UV radiation	Increased photosensitivity
Eccrine glands	Completely developed anatomically but functionally immature, more so in preterm neonates	Decreased response to thermal stress. Total anhidrosis in preterm neonates	Increased risk of hyperthermia
Hair follicles	Fewer terminal hairs in term and persistent lanugo hairs in preterm neonates		
Sebaceous glands	Hyperplasia due to stimulation by transplacentally transferred maternal androgens	Increased sebum secretion that normalizes by the next 4–6 weeks	Neonatal acne, seborrheic dermatitis and neonatal cephalic pustulosis are all attributable to this increased sebaceous gland activity in neonates

Abbreviations: TEWL, transepidermal water loss; UV, ultraviolet.

covered with more obvious and thicker lanugo hairs, which would otherwise be shed off about 4 weeks prior to term to be replaced by a second coat of shorter lanugo hairs seen in term newborns. The *small-for-date babies* have a wrinkled skin due to lack of subcutaneous fat and the skin (and vernix) at birth may be yellow-green due to staining by meconium. The finger nails are often long. The *postmature neonates* appear longer but otherwise have a similar appearance to that of the small-for-date babies. The vernix is often absent.

Hyperpigmentation In the dark-skinned newborns, a rather conspicuous hyperpigmentation predominantly involving the perineal [typically the scrotum **(Fig. 1)** and vulva] and periungal (base of the fingernails) areas may develop attributable possibly to stimulation by melanocyte-stimulating hormone in utero. Other less commonly involved areas include helix, nipple and areola, axillae and lower abdomen. The condition is transient and resolves spontaneously over sometime. Other infrequently described patterns of transient cutaneous hyperpigmentation of newborns include the *transient linear hyperpigmentation of newborn* and the *transient reticulated pigmentation of the new born*. The former involves the flexures of the limbs and abdomen and possibly represent an incomplete migration of melanocytes in the epidermis of the deepest part of cutaneous folds while the latter has been reported to involve the back and knees presumably as a result of post-traumatic hyperpigmentation in utero.

TRANSIENT SELF-RESOLVING CUTANEOUS AILMENTS

Vascular Phenomena

Erythema neonatorum Many of the healthy term infants develop a generalized striking erythema within a few hours that fades within a day or two. It is possibly attributed to higher levels of hemoglobin in the first week of life. This has to be differentiated from erythema toxicum neonatorum described below.

Acrocyanosis Cyanosis involving the perioral region and extremities (especially palms and soles) may occur in some of the term neonates which in absence of cyanosis of the central parts, is regarded as normal within the first 2 days. It becomes more obvious with reduction in surrounding temperatures, crying, or breath holding spells and disappears on re-warming. This physiological acrocyanosis appears to be due to an increased tone of peripheral arterioles, which in turn creates vasospasm, secondary dilatation, and pooling of blood in the venous plexuses.

Cutis marmorata (CM) A characteristic marbling of the skin in the form of reticulate bluish pattern **(Fig. 2)** on exposure to cold is a common occurrence in healthy neonates that readily disappears on rewarming. The trunk and extremities are involved symmetrically. The mechanism of development of CM is same as in acrocyanosis described above. Generally, CM disappears by the end of neonatal period but may, in some instances, persist for weeks to months without any clinical relevance. However, persistent CM beyond the neonatal period or the one which recurs may be a marker of Down syndrome, Edward syndrome, hypothyroidism and several others. A distinct negative pattern of mottling known as *cutis marmorata alba* may be seen in some cases due to constriction of deep vasculature.

Cutis marmorata telangiectatica congenita (CMTC), although resembles physiological CM, is a distinct entity in which the vascular mottling has a deep violaceous color, remains persistent even after rewarming and is associated with other cutaneous changes like atrophy and ulceration. Exact etiopathogenesis of CMTC is unclear but its significance lies in the fact that it forms a part of various syndromes (e.g. Adams-Oliver syndrome, phacomatosis pigmentovascularis type IV, etc.) and is also associated with various congenital anomalies (most common being limb hypoplasia).

Harlequin color change Harlequin color change is seen in about 10% of healthy newborns in whom an intense erythema on the dependent portion and pallor over the nondependent part with a clear demarcation between them develops when the baby is placed on one side. This change resolves immediately on placing the baby in supine position. It is of no pathological significance and possibly reflects the immaturity of the hypothalamic control over peripheral vascular tone. However, persistence of harlequin color change beyond 4th week may be indicative of hypoxia due to cardiovascular anomalies. It is also seen in neonates who have received general anesthesia or prostaglandin E2 infusion.

Manifestations of Circulating Maternal Sex Hormones

Neonatal acne Neonatal acne is not very uncommon and occurs within the first 2 weeks in most of the neonates. It may be congenital in about 20%. Neonatal acne is more common in male babies. The cheeks are the predominant sites affected, and closed comedones/papulopustular lesions **(Fig. 3)** rather than open comedones/cysts are the most common lesions. Stimulation of sebaceous glands by maternal androgens or transient fetal adrenal and gonadal androgen production is believed to be the cause for neonatal acne.

Figure 1 Physiologic hyperpigmentation of scrotum

Figure 2 Cutis marmorata
(*Source:* Dr Ahamadrasool Shirasangi, Consultant Pediatrician, Bagalkot, India)

Figure 3 Neonatal acne
(*Source:* Dr Ahamadrasool Shirasangi, Consultant Pediatrician, Bagalkot, India)

Figure 4 Erythema toxicum neonatorum

Furthermore, the testicular androgens stimulate primed adrenal glands which may partially explain the male preponderance. The lesions resolve spontaneously in the next 3 months without any treatment.

Sebaceous hyperplasia Circulating maternal androgens, or transient overproduction of fetal androgens exert a trophic effect on the sebaceous glands manifesting clinically as grouped tiny yellowish-white follicular papules without surrounding erythema concentrated over the nose, cheeks and upper lips. They are seen in up to 50% of term neonates and involute within the first few weeks postpartum.

Miniature puberty A constellation of transient clinical phenomena resulting from the influence of maternal and placental hormones on the fetus develop in the neonatal period collectively grouped as *miniature puberty*. Female genitalia appear well-developed with a conspicuous clitoral hypertrophy, mucoid vaginal discharge or even frank withdrawal bleeding beginning on 3rd or 4th day lasting for 2–3 days. The male genitalia similarly appear well-developed. Breast hypertrophy is seen in both the sexes at birth which subsides by the end of 4th week. In some babies, the breasts may engorge in the first 2–3 days with lactation of the so-called *witch's milk*. No intervention is needed.

Pustular Eruptions

Pustular eruptions in the newborn period include a host of conditions that include benign transient eruptions (describe below), infectious conditions and others. The transient eruptions, though themselves do not bear much clinical significance and resolve spontaneously, it is important, however, to differentiate them from other causes as described in **Table 2**.

Erythema toxicum neonatorum (Toxic erythema of newborn) Erythema toxicum neonatorum (ETN) is a common self-resolving papulopustular eruption seen in healthy newborns. The incidence of ETN increases with the gestational age as it is seen in more than half of term neonates and is rare in preterm neonates. It is characterized by erythematous macules, follicular papules and sterile pustules **(Fig. 4)**. The onset, in most of the cases, is between day 1 and day 4 and the rash resolves within 4 days without any treatment. The trunk is the most favored area; although, the face and extremities may also be involved while the palms and soles are spared. There is no gender or racial predilection. A characteristic feature is the presence of peripheral eosinophilia as well as predominant eosinophilic infiltrate in the follicular infundibulum. The exact etiology of ETN is unknown. While some believe it to be a

Table 2 Pustular eruptions in newborns

Transient conditions	Erythema toxicum neonatorum Transient neonatal pustular melanosis Infantile acropustulosis Eosinophilic pustular folliculitis Miliaria pustulosa
Infectious conditions	*Bacterial:* Staphylococcal infections Streptococcal infections *Pseudomonas* infection Neonatal listeriosis Congenital syphilis *Viral:* Neonatal herpes simplex Varicella zoster infection *Fungal:* Congenital candidiasis Neonatal cephalic pustulosis Pityriosporum folliculitis
Neoplastic disorders	Langerhans cell histiocytosis Urticaria pigmentosa
Inherited disorders	Acrodermatitis enteropathica Incontinentia pigmenti
Others	Pustular psoriasis Scabies

response of neonatal skin to mechanical or thermal stimuli others consider it as an immune response to microbial colonization of the hair follicles. It is also proposed to be a form of graft-versus-host reaction caused by materno-fetal transfer of lymphocytes during or before delivery that react with some of the baby's antigens. An association with dyspepsia that leads to absorption of enterotoxins with subsequent development of rash (hence the name *toxic erythema*) has also been advocated.

Transient neonatal pustular melanosis (TNPM) Transient neonatal pustular melanosis is characterized by superficial noninflammatory vesicopustules that easily rupture to form crusts surrounded by a collarette of scale. These scaly lesions are later replaced by postinflammatory hyperpigmentation that resolves gradually over several weeks. The exact etiopathogenesis is unclear and it has been thought to be a variant of ETN. In some cases, the presentation may be with hyperpigmentation suggesting that the

previous stages occurred in utero. TNPM differs from ETN in being congenital, affecting the chin, neck and shins more commonly than the trunk, and the lesions showing predominant neutrophilic infiltrate. The incidence is more common in term infants of African descent without any gender preference. As with ETN, no treatment is required.

Infantile acropustulosis (IA) An uncommon eruption, usually occurring between 3 and 6 months of age but can be seen at birth or neonatal period characterized by recurrent crops of intensely pruritic, acrally located (including palms and soles) papulopustular lesions is termed as infantile acropustulosis. The lesions last for 7–14 days and recur in 3–4 weeks. With time, the intensity and frequency of the rash decrease with eventual spontaneous resolution by 3–4 years. The exact etiology is not known but IA is thought to a post-scabetic hypersensitivity reaction. Indeed, infantile scabies is a differential diagnosis for IA and mineral oil examination must be carried out in these cases. However, the characteristic burrows of scabies are not present. A smear prepared from the pus reveals predominantly neutrophils. Potent topical steroids in mild-to-moderate cases and systemic dapsone in recalcitrant cases prove successful.

Eosinophilic pustular folliculitis of infancy (Ofuji disease) Ofuji disease is a rare disorder affecting almost exclusively the boys. It is characterized by recurrent crops of papulopustular lesions commonly involving the face and scalp and occasionally the trunk and extremities which evolve through a crusting phase to heal without any residua. The presentation may be at birth or in the first few weeks with spontaneous resolution occurring in a few months. Peripheral eosinophilia and numerous eosinophils in the pustular contents are helpful in the diagnosis. Treatment is mainly symptomatic.

Others

Superficial cutaneous desquamation Superficial desquamation is seen in more than 75% of the term neonates that begins at 24–36 hours of age. It initially begins at the ankles and may remain localized or become widespread. Traditionally, this type of desquamation was believed to be rare in preterm and very obvious in post-term babies. However, Rivers et al. (JAAD, 1990) observed that this phenomenon occurs with equal prevalence at all gestational ages. Superficial desquamation is always much more severe in small-for-date babies irrespective of their gestational age. Severe and excessive desquamation at birth or in the early neonatal period may be indicative of congenital ichthyosis and X-linked hypohidrotic ectodermal dysplasia.

Sucking blisters Vigorous sucking *in utero* leads to development of flaccid blisters at the affected site and is a common occurrence. Most commonly the radial forearm, wrists and fingers are involved either unilaterally or bilaterally. Presentation at birth may be with intact blisters or with erosions and callosities which subside spontaneously within a few days.

Hair changes During the 5th month of intrauterine life, there is a synchronous shedding of the entire scalp hair that regrow and enter telogen phase in a wave from front to back beginning at about 12 weeks before term. After shedding of these telogen hairs from the frontal and parietal areas, the follicles again enter the anagen phase in a similar pattern from front to back. However, the follicles in the occipital region do not enter telogen until term and, therefore, a rather conspicuous alopecia may appear at this site due to shedding of these telogen hairs in the early neonatal period.

In some babies, there is an unusually diffuse hair loss during the neonatal period (telogen effluvium of the newborn) and by the end of 6 months, most babies have regrown all the hair. At this stage, hairline often extends to the lateral ends of the eyebrows, but the

terminal hairs comprising this extension are gradually converted to vellus hairs during the remainder of the first year, causing the hairline to recede to its characteristic childhood position.

Milia Milia are characterized by multiple tiny whitish-yellow papules that represent miniature epidermal cysts derived from pilosebaceous follicles **(Fig. 5)**. These are seen in 30–50% of the neonates and get extruded by themselves in a few weeks. Milia are also seen involving the hard palate (Epstein's pearls) and alveolar margins (Bohn cysts) in majority of newborns which behave in the same manner as cutaneous milia. Large, extensive milia that are persistent and involve atypical sites may be indicative of orofacial-digital syndrome type I, Marie-Unna type congenital hypotrichosis or the X-linked Bazex-Dupré-Christol syndrome.

Miliaria Miliaria results due to blockage of eccrine ducts and is a frequently encountered transient ailment affecting about 15% of the newborns. It is commonly associated with hot humid surroundings and friction, and resolves spontaneously on cooling. Depending on the level of obstruction of the eccrine duct, three clinical forms are described—(1) miliaria crystallina (block at subcorneal level), (2) miliaria rubra (block in the malpighian layer), and (3) miliaria profunda (block at the dermoepidermal junction). Miliaria crystallina is characterized by noninflammatory clear flaccid vesicles on the forehead, neck and other occluded areas which are commonly seen on 6th or 7th day of life. Miliaria rubra appears as erythematous papules due to associated inflammation **(Fig. 6)** as a result of seepage of the ductal contents into the dermis. These lesions typically appear between 11th and 15th day and are often associated with discomfort. Sometimes the inflammation is intense enough to produce pustular lesions (miliaria pustulosa). Miliaria profunda is characterized by larger fleshy papules or nodules involving the trunk. In type I pseudohypoaldosteronism, miliaria pustulosa (pustular miliaria rubra) is considered to be a specific finding.

PATHOLOGICAL SKIN CHANGES IN NEONATES

Seborrheic Dermatitis
The infantile seborrheic dermatitis, distinct from the adult form, begins commonly in the first month of life and clears by the age of 6 months. Excessive sebum production and *Malassezia* species' colonization are implicated in the pathogenesis but not proven unequivocally. The congenital form manifests as thick yellowish or whitish greasy adherent plaque mostly involving the vertex and

Figure 5 Milia
(*Source:* Dr Ahamadrasool Shirasangi, Consultant Pediatrician, Bagalkot, India)

Figure 6 Miliaria rubra
(*Source:* Dr Ahamadrasool Shirasangi, Consultant Pediatrician, Bagalkot, India)

Figure 7 Infantile seborrheic dermatitis presenting as *cradle cap*

frontal regions [cradle cap **(Fig. 7)**]. The acquired form develops on previously clear scalp and is associated with involvement of body folds like neck, axillae, groins where the lesions are more inflamed and macerated. At this stage, infantile seborrheic dermatitis is difficult to differentiate from atopic dermatitis and inverse psoriasis. However, the prognosis of infantile seborrheic dermatitis is excellent with resolution occurring in a few weeks even without treatment and mild topical steroids are helpful for faster clearance.

Psoriasis

Psoriasis in the neonatal period is, in general, uncommon. The common forms of psoriasis at this age are the napkin psoriasis (presenting as diaper dermatitis) and much rarer pustular psoriasis. Although rare, congenital psoriasis is also described. Sometimes infantile psoriasis may involve the scalp and face when a differentiation from infantile seborrheic dermatitis is possible only by biopsy. Koebner's phenomenon is common and nail changes are seen in 10% of the cases. Pustular psoriasis may present at birth or in the few weeks after birth. Presentation is often with fever and sheets of small pustules. Annular or circinate forms may also be seen. Associated findings include geographic tongue, sterile osteomyelitis, and very rarely pulmonary involvement with the capillary leak syndrome.

Napkin Dermatitis

An inflammatory rash involving the diaper area is commonly encountered between 3rd and 12th week, which is considered to be an irritant contact dermatitis because of prolonged contact with feces and urine. It is exceedingly rare in the absence of napkin wearing and other associated factors like maceration by water, friction, frequent urination, diarrhea, pancreatic proteases and lipases in feces, ureases produced by fecal bacteria, use of broad spectrum antibiotics and developmental anomalies of urinary tract. The most common presentation is with confluent erythema of the convexities in the closest contact with the napkin (buttocks, genitalia, lower abdomen, pubic area and upper thighs) with sparing of deeper parts of the groin flexures. Sometimes the eruption may be confined to the margins of the napkin area (tidemark dermatitis) or present as an erosive form with small vesicles and erosions which develop into shallow, round ulcers (Jacquet's dermatitis). Several distinctive variants have been observed. Secondary infection by *C. albicans* is common when the rash is surrounded by satellite pustules. Diaper dermatitis may be an early feature of atopic dermatitis or infantile seborrheic dermatitis.

Treatment includes use of good quality napkins with a topsheet impregnated with an emollient, frequent changing of napkins, and use of mild topical steroids or anti *Candida* antifungals as indicated.

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis (SCFN) presents as asymptomatic or tender erythematous and indurated plaques or nodules due to focal areas of fat necrosis appearing in the first month of life with characteristic histological features. The condition is rare and self-limiting and is seen with predispositions like maternal diabetes, perinatal asphyxia, hypothermia, hypoxia, neonatal infections and other causes. The neonatal fat undergoes crystallization more readily in presence of hypothermia leading to fat cell damage and granulomatous reaction. The cheeks, back, buttocks and arms are the frequently involved sites. Skin biopsy shows an infiltrate of lymphocytes, histiocytes and fibroblasts, with necrosis of fat and multinucleated giant cells. Doubly refractile crystals can be seen under polarized light. Calcium deposits and eosinophilic granules are also common.

Cold Panniculitis

Painful red, indurated nodules developing on exposure to cold climate occurs in newborns attributable to thermally induced damage and necrosis of subcutaneous fat as in SCFN. Induration resolves over a period of a week or so, often with postinflammatory hyperpigmentation.

Sclerema Neonatorum

Sclerema neonatorum is a condition characterized by a rapidly spreading nonedematous skin hardening seen most commonly in preterm neonates who are severely ill with poor perfusion. Hypothermia, metabolic acidosis, sepsis, cardiovascular disease, pulmonary hemorrhage, central nervous system abnormalities, and glucose or electrolyte imbalances have been implicated in the pathogenesis. Neonatal sepsis, however, is the most commonly encountered predisposing factor. Thickening initially begins over the buttocks and thighs which rapidly spreads to involve the entire body except for the palms and soles. Reduced chest expansion and flexion deformities of joints may be seen. The scleredermatous skin shows higher concentration of saturated fatty acids which solidify easily in presence of hypothermia and impaired perfusion. Treatment is mainly aimed at removal of underlying cause at the

earliest. However, the prognosis of sclerema neonatorum is usually guarded.

Neonatal Purpura Fulminans

Purpura fulminans is a potentially life-threatening, progressive condition characterized by hemorrhagic necrosis of skin due to cutaneous vascular thrombosis. In the neonatal period, it almost always is indicative of congenital homozygous or compound heterozygous deficiency of protein C or S. The condition manifests within a few hours to 5 days of birth characterized by noninflammatory retiform purpura which later coalesce to form large hemorrhagic bullae and necrotic eschar. The pressure points like the buttocks and lower extremities are involved initially and in severe cases mucosal surfaces and internal organs may also be affected. In addition, the neonates are at increased risk of cerebral and retinal vessel thromboses. Unlike with acute infectious purpura fulminans, patients with congenital protein C or S deficiency are often hemodynamically stable and afebrile at presentation unless the condition is precipitated by an infection. Treatment must be prompt and timely, and involves supportive measures with administration of protein C and S either with fresh frozen plasma or protein C/S concentrate followed by oral long-term oral anticoagulants.

Blueberry Muffin Baby

Blueberry muffin baby refers to a newborn that is born or presents in a few days with firm, nonblanchable, bluish-magenta colored papulonodules involving preferentially the head and neck region. These lesions represent persistent dermal erythropoiesis which, in the prevaccination era was commonly a feature of congenital rubella. However, many other vertically transmitted infections present with such lesions, so do many of the hematological and neoplastic disorders **(Table 3)**. The lesions evolve into dark purple to brownish macules and fade away spontaneously within 2–6 weeks. Babies with multiple vascular disorders, such as hemangiopericytoma, hemangioma, blue rubber bleb nevus syndrome and glomangioma may be mistaken for *blueberry muffin* baby. Investigations must include complete blood analysis, TORCH screening, viral cultures, and a Coombs test. A skin biopsy is not always indicated but is helpful if an underlying neoplastic disease is in question. Specific treatment is guided by the underlying disease.

Table 3 Causes of blueberry muffin baby

Extramedullary (Dermal) hematopoiesis	*Congenital infections:* Toxoplasmosis Rubella Cytomegalovirus Herpes simplex Coxsackievirus Parvovirus *Hematological disorders:* Hemolytic disorders (ABO/Rh incompatibility, hereditary spherocytosis, etc.) Twin-twin transfusion Erythroblastosis fetalis
Neoplastic disorders	Transitory myeloproliferative disease Neuroblastoma Langerhans cell histiocytosis Congenital leukemia Congenital alveolar cell rhabdomyosarcoma
Other disorders	Hemangiomatosis Multifocal lymphangioendotheliomatosis Glomuvenous malformations

Infections

Infections in neonatal period can be those that are transmitted vertically, acquired during passage through an infected birth canal, or those that are acquired from external environment after birth.

Staphylococcal scalded skin syndrome Staphylococcal scalded skin syndrome (SSSS) is an inflammatory toxin-mediated generalized desquamating disorder caused by *Staphylococcus aureus*, most commonly by the phage group 2 types 71 and 55 that produce *Epidermolytic toxin A* and/or *B* which target *Desmoglein 1*, an intercellular adhesion molecule leading to acantholysis. SSSS is common in neonates, attributable to the inefficient metabolism and renal excretion of the toxin which is produced at foci of infections like the umbilicus, breast, and conjunctiva. The disease is characterized by erythema and tenderness of the skin which later develops flaccid bullae and exfoliation. SSSS in older children is discussed in the Chapter 48.3. Specific treatment of SSSS involves administration of a penicillinase resistant penicillin analog like flucloxacillin or methicillin, or with an appropriate cephalosporin or sodium fusidate with the route of administration guided by the severity of the disease.

Ecthyma gangrenosum Ecthyma gangrenosum is a potentially fatal illness caused by *Pseudomonas aeruginosa* which is common in the hospital environment and infections are encouraged by widespread use of broad spectrum antibiotics. In the neonatal period, ecthyma gangrenosum is seen in the setting of prematurity or immunodeficiencies. Although, classically ecthyma gangrenosum is a cutaneous manifestation of pseudomonal septicemia, in premature neonates the lesions may be seen at the site of inoculation without bacteremia. The lesions are characterized by tense hemorrhagic vesicles or bullae with a typical violaceous hue that rupture to form ulcers with central necrotic eschar. Anogenital area and extremities are frequently involved sites. Infection is potentially dangerous when it occurs in the setting of septicemia. Treatment is with intravenous antipseudomonal penicillins or third generation cephalosporins. Even with early treatment, mortality is generally high.

Neonatal herpes simplex Majority of neonatal herpes simplex virus (HSV) infection are caused by HSV 1 and 2 that is acquired through contact with an infected birth canal. Intrauterine infection can also occur either through transplacental transmission or ascending infection. HSV infection in newborns is a potentially serious disease with possible mortality. The lesions appear between day 2 and 20 involving the skin and/or mucousa, unless intrauterine infection has occurred when lesions are seen at birth. Isolated or grouped vesicles on an erythematous base are the most common skin lesions that commonly involve the face and scalp. Mucosal lesions present as erosions on the tongue, palate, gingivae and buccal mucosa. Systemic involvement in the form of meningitis may occur when the mortality and long-term complications are more likely even with appropriate antiviral therapy. Early diagnosis and acyclovir therapy prevents dissemination of the infection when it is confined to the skin.

Fetal varicella syndrome Varicella contracted for the first time during pregnancy has a 25% chance of getting transmitted to the fetus and when the infection occurs in early pregnancy, spontaneous abortion occurs or in about 2% or the child is born with a variety of congenital anomalies collectively termed as fetal varicella syndrome. These including hypoplastic limbs (unilateral and involving the lower extremity), cutaneous scarring (often dermatomal), ocular anomalies (chorioretinits, microphthalmia, Horner syndrome) and CNS anomalies (seizures, mental retardation, encephalitis, dorsal radiculitis). Pregnant women exposed to varicella zoster virus for the first time should receive

varicella zoster immunoglobulin (VZIG) which appears only to modify clinical varicella but does not prevent fetal infection. When a nonimmune pregnant woman develops varicella 4 days on either sides of delivery, the infection may be transmitted to the newborn that carries a mortality rate of up to 30%. Such cases should be managed by VZIG.

Candidiasis Congenital candidiasis is a rare condition which reflects maternal *Candida* chorioamnionitis resulting from the ascending infection from the genital tract. Congenital candidiasis is characterized by presence of widespread discrete erythematous macules and papules at birth that progress to vesiculopustular lesions in the next few days. Palmoplantar pustules are regarded as hallmarks of congenital cutaneous candidiasis. The lesions of congenital candidiasis are confined to skin in majority of the cases. However, in preterm neonates mucosal lesions may coexist and in very low birthweight babies such lesions may disseminate systemically. Appropriate anticandidal antifungal therapy is enough for patients with cutaneous lesions only. Amphotericin B is the drug of choice for systemic candidiasis.

Neonatal candidiasis is acquired from an infected birth canal and presents as oral candidiasis, with or without napkin candidiasis presenting as a moist *beefy-red* plaque often with satellite pustules. Neonatal candidiasis is effectively managed by topical antifungals. These have been discussed in Section 33.

Congenital Nevi and Hamartomas

Nevi and hamartomas in the neonatal period are mostly congenital and may occur as isolated lesions or be associated with other anomalies or as features of a syndrome.

Verrucous epidermal nevi These keratinocytic hamartomas present at birth affecting both the sexes equally. Initial appearance is that of a slightly pigmented streak or plaque which becomes darker and verrucous with age. In most of the cases the lesions are linear following the lines of Blaschko; although, a systematized form affecting larger body surface area bilaterally is described. Treatment depends upon the type of the lesion and extent of involvement. Ablative procedures with cryotherapy, carbon dioxide or neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers are probably most effective treatment options than topical retinoids or keratolytics for linear lesions. For systematized or extensive lesions, systemic retinoids are helpful but recurrence is common with discontinuation of treatment.

Nevus sebaceous Nevus sebaceous is an epidermal hamartoma comprised of sebaceous glands presenting at birth with equal gender predilection. Head and neck regions are most commonly involved with a greater tendency to affect the scalp. In the neonatal period, it appears as a circumscribed area of alopecia with a velvety texture and yellowish to fleshy color that remains unaltered until adolescence when it grows and becomes lobulated due to androgen stimulation. Histopathological findings in infancy and childhood are similar to those of verrucous epidermal nevus with sparse immature sebaceous glands. However, presence of cords and buds of poorly differentiated epithelial cells representing primordial pilosebaceous follicles are diagnostic features at this stage. Surgical excision is the treatment of choice.

Congenital smooth muscle hamartoma Congenital smooth muscle hamartoma originates from smooth muscle fibers of the erector pili muscle. It is often congenital, but an acquired form is also seen. It is usually a solitary lesion occurring on the trunk or proximal extremities with predilection for the lumbosacral area. Clinically, it presents as a skin colored or slightly pigmented patch or plaque with hypertrichosis which becomes more obvious and slightly elevated on stroking (the *pseudo-Darier* sign). Histopathologically it is composed of proliferating smooth muscle bundles of the

erector pili muscle in the reticular dermis. Surgical excision is curative.

Congenital melanocytic nevi Congenital melanocytic nevi (CMN) are present at birth and are characterized by well-defined deeply pigmented macules or patches that proportionately grow with the child. Depending on the size, CMN are classified into small (< 1.5 cm), medium (1.5–19.9 cm), large (≥ 20 cm) and giant. Large and giant CMN are, associated with malignant potential. Large and giant CMN preferentially involve the lower back (bathing trunk nevus). With age, they develop surface rugosities, hypertrichosis and the color intensifies as well. Satellite lesions also develop. Treatment of small CMN may not be necessary. Management of giant CMN is difficult and involves surgical approaches like serial excision with tissue expansion techniques and skin grafting.

Dermal melanocytoses Dermal melanocytoses refer to the dermal melanocytic nevi which develop as a result of arrest in the migration of melanocytes in their journey from the neural crest to the skin. These include Mongolian spots, nevus of Ota and nevus of Ito.

Mongolian spots They present as ill-defined bluish or slate-gray macules and patches at birth. They appear as a single patch or as multiple lesions commonly involving the lumbosacral region. Extrasacral sites include buttocks, shoulders or extremities **(Fig. 8)**. The color deepens for a period after birth peaking at 2 years of age and then disappears gradually by the first decade. Mongolian spots are also associated with inherited syndromes like phacomatosis pigmentovascularis (types II, IV, and V) and Sjögren-Larsson syndrome. Large and extensive lesions are associated with GM1 gangliosidosis type 1, Hunter and Hurler syndromes, and trisomy 20 mosaicism. Such lesion do not regress until about the second decade and Q-switched ruby laser or Q-switched Nd:YAG lasers have been used successfully in these cases.

Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris) It is characterized by unilateral bluish-gray macules and patches in a dermatomal pattern affecting the skin supplied by the first and second division of trigeminal nerve. In half of the cases it is congenital and appears during the second decade of life in the rest. The lesions are persistent and may darken at puberty. Q-switched Alexandrite laser is useful for treatment. *Nevus of Ito* is similar to nevus of Ota and involves the acromioclavicular region. It occurs in the areas innervated by the posterior supraclavicular and lateral cutaneous brachial nerves.

Figure 8 Aberrant Mongolian spot involving the extremity
(*Source:* Dr Ahamadrasool Shirasangi, Consultant Pediatrician, Bagalkot, India)

Congenital Defects

Aplasia cutis congenital Aplasia cutis congenita is characterized by a circumscribed area of absent skin with a predilection for the midline of vertex of scalp. It may occur as an isolated defect or in association with other developmental anomalies. Possible causes for this condition include genetic factors, vascular compromise, trauma, teratogens and intrauterine infections. Clinically aplasia cutis congenita may present as erosion, a deep ulcer, a scar, or the most common membranous form in which the defect is covered by a thin, translucent membrane. A rim of long coarse hair may be present along the margin of the defect (hair collar sign), which is a relatively specific marker of an associated neural tube defect. Lesions may appear bullous due to the presence of serous fluid within the membrane. The lesions eventually flatten leaving behind an atrophic scar.

Supernumerary digits These occur as isolated anomalies and show an autosomal dominant inheritance pattern. They appear as small fleshy or warty papules most commonly on the ulnar side of the fifth digit. They are present at birth, often bilaterally. Histologically, they are composed of nerve fiber fascicle. Larger lesions may contain cartilage or a vestigial nail. Surgical excision is advised when removal is desired.

Supernumerary nipples Supernumerary nipples are the most common type of accessory mammary tissue found in 1–6% of the population with equal sex predilection. Although usually sporadic, about 10% of cases are familial. Supernumerary nipples are most commonly seen on the inframammary chest as a small, soft, pink or brown papule, either with a surrounding areola. However, they may be located anywhere along the milk line. Lesions are most often single, but they may be multiple and/or bilateral. Supernumerary nipples are found in several multiple congenital anomaly syndromes, including Simpson-Golabi-Behmel syndrome, cleft lip/palate-ectodermal dysplasia syndrome and tricho-odonto-onychial dysplasia.

Cutaneous markers of spinal dysraphism As the skin and nervous system share an ectodermal origin, coexistence of anomalies of the structures is often seen. Midline cutaneous lesions are seen in more than 80% of cases with closed spinal dysraphism serving as a valuable marker for spinal dysraphism, and, in the majority of patients, they are the finding that leads to the diagnosis. Most of the cutaneous lesions associated with spinal dysraphism are located in the lumbosacral area, reflecting the relative rarity of neural tube defects in the cervicothoracic region. Sacrococcygeal dimples, lipoma in the midline, midline localized hypertrichosis (faun tail) and also midline hemangiomas comprise such markers and their presence at birth must alert the clinicians.

MORE ON THIS TOPIC

Adya K, Palit A. Neoplastic Disorders of Skin. In: Inamadar AC, Palit A, Ragunatha S. Text Book of Pediatric Dermatology. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2014. pp. 495-512.

Adya KA, Inamadar AC, Palit A. Reticulate dermatoses. Indian J Dermatol. 2014;59:3-14.

Adya KA, Inamadar AC, Palit A, Shirasangi A. Miniature puberty in an 8-day-old female neonate. Indian J Pediatr. 2014;81:1266-7.

Cohen BA. Neonatal Dermatology. In: Cohen BA, (Ed). Pediatric Dermatology. 3rd ed. Philadelphia: Elsevier Mosby; 2005. pp. 15-66.

Gelmetti CM, Grimalt R. Infantile seborrheic dermatitis. In: Irvine A, Hoeger P, Yan A. Harper's Textbook of Pediatric Dermatology, 3rd ed. Oxford: Wiley-Blackwell; 2011. pp. 35.1-35.8.

Lee RSY, Wan HS, Chan RL. Harlequin colour change in a newborn with meningitis. Hong Kong Med J. 2012;18:539e3-e4.

Lucky AW. Transient benign cutaneous lesions in the newborn. In: Eichenfield LF, Frieden IJ, Esterly NB. Neonatal Dermatology, 2nd ed. Philadelphia: Saunders Elsevier; 2001. pp. 85-97.

Paige DG, Gennery AR, Cant AJ. The neonate. In: Burns T, Breathnach S, Cox N, Griffiths C. Rook's Textbook of Dermatology, 8th ed. Oxford: Wiley-Blackwell; 2010. pp. 17.1-17.85.

Paller AS, Mancini A. Cutaneous disorders of the newborn. In: Paller AS, Mancini A. Hurwitz Clinical Pediatric Dermatology, 4th ed. Edinburgh: Elsevier Saunders; 2011. pp. 10-36.

Rovatti G, Cutrone M. Cutaneous hyperpigmentation of the distal digits. A transient neonatal dermatosis. Eur J Pediatr. Dermatole. 2000;10:137-40.

Chapter 48.2
Care of Skin in the Newborn
S Sacchidanand, Preeti Sheth

The skin acts as a barrier against mechanical, chemical and thermal injuries, penetration of toxins and infections, and prevention of fluid and electrolyte imbalances. It also provides thermoregulation, fat storage and insulation. It provides tactile sensation and promotes immune surveillance. As the neonate is exposed to a dry, external, aerobic world from a sterile, aquatic, uterine environment, the skin undertakes important developmental changes. Also, though the function of the skin barrier is believed to begin in utero, it is actually an ongoing process for up to 12 months after birth. Hence, it is extremely essential to preserve the integrity of the skin in the neonatal age group, and hence the importance of newborn skin care.

The skin of the newborn exhibits certain differences from adult skin **(Table 1)**. Anatomically, the body surface area of the neonate is much higher (700 cm^2/kg) as compared to that of an adult (250 cm^2/kg); the skin is relatively much thinner and delicate; the dermo-epidermal junction is weaker, and the barrier of the skin is not well-formed, making the penetrability of the stratum corneum much higher. Also the sweat and sebaceous glands though large in number, are immature and less active. As a result of these anatomical differences in a newborn, there is increased transepidermal water loss (TEWL), leading to increased absorption of toxins and infectious agents, fluid and electrolyte loss, and impaired thermoregulation and blisters are formed due to the

Table 1 Structural differences between newborn and adult skin

Skin component	Adult	Full-term newborn	Preterm newborn
Epidermis	Normal	Strong stratum corneum	Few, thin layers of stratum corneum
Dermis	Normal	Thin	Thin
Dermo-epidermal junction	Strong coherence between epidermis and dermis	Weak coherence	Weak coherence
Hair type	Vellus and terminal	Vellus	Lanugo
Sweat glands	Functionally mature	Immature	Immature
Sebaceous glands	Structurally and functionally mature	Mature	Mature
Penetration	Strong barrier impeding infiltration	Penetration and absorption of substances present	Immature barrier function leading to increased infiltration and absorption of substances
pH	5.5	> 6	> 6
Body surface area	x	3x	7x

x, body surface area in adults

weak compatibility of the epidermis and dermis. Furthermore, the skin of the premature newborn demonstrates even weaker barrier functions and weaker apposition between epidermis and dermis, leading to ten times higher TEWL and disastrous consequences.

BARRIER FUNCTION OF SKIN

The barrier function of the skin pertains to the uppermost layer of the epidermis, namely the stratum corneum. It is composed of keratinocytes which are placed in a mold of lipids, which in turn are made up of cholesterol, ceramides and fatty acids. These are the natural moisturizing factors of the skin. A different set of lipids which collaborate with water, forming a hydrophilic film at the surface of the epidermis, also contribute to maintain the moisture balance of the skin.

The pH of the skin is close to neutral at birth, which rapidly becomes acidic (pH 5.4–5.9) in a term baby (few days), but takes a longer period of time in case of preterm babies (many weeks). This *acid mantle* of the skin is essential as it possesses antimicrobial properties, and raising the skin pH increases the microbial colonization, leading to infections. Detergents, soaps, chemicals, and even water are known to raise the pH of the skin. Hence, skin care practices are imperative to maintain the integrity of the skin and its acid mantle.

Huffines and Logsdon developed a scale called the Neonatal Skin Risk Assessment Scale (NSRAS), to study the breakdown of the skin, which also follows the Braden Scale for Predicting Pressure Sore Risk. The NSRAS has six components: general physical condition, mental state, mobility, activity, nutrition and moisture. Each component is given 1 point for a total of 6 through 24, with a higher score representing a lower risk.

Hygiene of the Caregivers
A very common cause of nosocomial infection is believed to be the caregiver's or attendant's hands. Handwashing is the easiest and economical way of breaking this cycle. After every patient contact, one must wash the hands with a mild, skin cleanser, following which one must apply an emollient to maintain the softness and suppleness of the skin.

Vernix Caseosa
Vernix caseosa is an inherently occurring, yellowish-white film that covers the entire skin surface of the newborn. Its major constituents are water 81%, lipid 19% (epidermal triglycerides and cholesterol; and dermal-squalene and waxes), and proteins 10% (sebaceous secretions, shed fetal corneocytes). It begins to form at 17–20 weeks of gestation, becomes thick by 36–38 weeks, and regresses later to be found only in the creases by 40 weeks. Hence, it is found only in term babies, and not in preterm or post-term babies.

Vernix caseosa serves as a lubricant during delivery, and also has essential hydration, thermoregulation, antibacterial and wound healing properties. The protein composition of vernix comprises of lysozyme, lactoferrin, cystatin A, cathelicidins and defensins. It also contains cytokines like IL1a, IL1b, TNFα and IL-67, which help to form the barrier of the skin, and free amino acids like asparagine and glutamine.

CLEANING THE SKIN

Bathing
Bathing is the best possible way of clearing the newborn of vernix, blood and meconium, and also reducing the exposure to the maternal blood and body fluids, thereby minimizing the risk to HIV and hepatitis B viruses. In a full-term baby, the first bath is given 2–6 hours after birth, once the temperature and hemodynamic

parameters are stable, as bathing may lead to hypothermia, respiratory distress and unstable vital signs. The temperature of the water should not exceed 37°C, and the bath should not be more than 5 minutes. An extended bath not only increases the hydration of the skin, but also can lead to more friction. As far as a low birthweight newborn is concerned, it is better to defer the bath till the cord has fallen off.

Pure and clean water is enough for the first bath. Soaps and cleansers are not required for the initial few weeks. Immersion bathing (keeping the entire body of the infant in a tub of water, except the head and neck) is preferable, as the newborns shows less fluctuation in the vital parameters and preserves heat more. Caregivers may wear gloves, for the first bath, to minimize touch with blood on the newborn's skin. Areas such as face, neck, diaper area and flexures need special attention while bathing. Once the newborn is bathed in a warm ambience, he should be instantly dried from top to bottom, swaddled in a warm, dry towel, and placed next to the mother.

Bathing can be quite a relaxing and soothing venture for the baby, which also helps to increase its bond with the mother. It is not only a fun experience for the infant, but also helps develop a bond with parents and other caregivers. **Box 1** gives the recommendations for bathing that need to be followed.

Cleansing Agents

Cleansing removes dirt, microorganisms, sweat, sebum and corneocytes from the skin surface. Water is not considered the ideal cleanser for the skin of the newborns, as it increases the skin pH from 5.5 to 7.5, which facilitates the breakdown of the skin barrier and also does not remove lipophilic substances like sebum and feces. Hence, the introduction of cleansers and soaps.

An ideal cleanser is one which is gentle, having a neutral pH, and is fragrance, dye, and preservative-free. The major constituent of a cleanser is a surfactant or detergent, which helps in removing fat-soluble impurities from the skin. This is achieved by its foaming properties and also by reducing the surface tension between air and water. However, this action denatures the proteins, robs the skin of its lipids and moisture and increases the pH, which finally leads to irritation, and a dry, rough, flaky skin. Therefore, syndets or synthetic detergents, which are replacements to soaps, are preferred in the neonatal age group as they are less harsh. These have a pH which is nearer to that of normal skin and do not disturb the normal microflora.

Moisturizers like glycerin, paraffin or mineral oil are also added to soaps to hydrate the skin and make it smooth and soft. Liquid cleansers are available which clean without water. They contain both surfactants and emollients. These are rubbed into the dry skin to form lather followed by wiping off the area with a cloth.

BOX 1 Recommendations for bathing

- Dry the infant immediately after delivery
- Gently remove blood and meconium
- Vernix to be allowed to dry and shed on its own
- First bath to be given once the temperature stabilizes
- Bathing is preferred over cleaning with cloth
- Depth of water up to infant's hips
- Bathing to be for only 5 minutes
- Temperature of water should not exceed 37–37.5°C
- Ambient air temperature should be 21–22°C
- Bathing in the evening relaxes the baby and promotes sleep
- Frequency of bathing is 2–3 times per week until the baby begins to crawl or as demanded by local culture and tradition
- Liquid cleansers can clean and moisturize the skin better than water alone.

Nowadays, caregivers use cleaning wipes as they are easy to use and are nonodoriferous. But these are not recommended as they contain soap and cause delipidation and barrier damage.

Skin Antisepsis

The California Perinatal Quality Care Collaboration has recommended the use of chlorhexidine and povidone-iodine for antiseptic purposes in a newborn. The risk of infection and mortality increases in the newborn period, as the epidermal barrier is not fully mature, allowing the percutaneous invasion of the pathogens.

Chlorhexidine is an effective antiseptic agent as its action covers gram-positive and gram-negative organisms, yeasts and few viruses. Tielsch et al. demonstrated that chlorhexidine cleansing of the skin of low birthweight infants, immediately after delivery, reduced the mortality by 28%. The reduced systemic absorption and increased local potency is attributed to its strong adherability to the skin. However, it may cause skin irritation and systemic absorption and data regarding its safety and efficacy in the newborn age group is unavailable. Hence, it is not approved by the US Food and Drug Administration for use in infants less than 2 months old.

Another commonly used topical antiseptic is povidone-iodine, but it is known to cause necrosis of skin and hypothyroidism, and hence, should be used with caution. One more agent that is used is alcohol, but it causes dryness of the skin, systemic absorption and is considered to be less efficacious than chlorhexidine and povidone-iodine.

Emollients

Emollients or moisturizers or lubricants are agents which make the skin soft and supple. The basic constituents of an emollient are lipids, which could be of vegetable or animal origin, or may be derived from mineral oils. They could be synthetic in nature too. Different types of emollients are hydrocarbons (vaseline, paraffin), waxes (bees wax, lanolin), fatty substances (cetyl or stearyl alcohol), and oils (coconut oil, olive oil, mustard oil, ground nut oil, mineral oil, synthetic oil). Emollients are available in two types of formulations: ointment or cream based. In a hot and humid climate like ours, ointments lead to occlusion, hence creams are naturally preferred. The advantages of applying an emollient in the newborn period are as follows:

- Maintains the barrier function of the epidermis
- Reduces the TEWL
- Reduces the entry of invasive pathogens
- Improves skin hydration and condition
- Reduces hypothermia and scaling of the skin
- Provides nutrition via transcutaneous absorption of lipids
- Plays an important role in massage and forms a bond between mother and child.

Coconut oil is used widely across India through generations, as it has been an ideal moisturizer for dry skin with its small molecular nature and easy penetrability. It is also cheap and easily available. Nut-based oils should be avoided. A randomized double-blind controlled study in Philippines demonstrated that both coconut oil and mineral oil were effective in improving the skin hydration and were also safe to use.

Baby Powders

Powders are not advisable in the neonatal age group, even though they take-up the sweat and moisture in the flexural areas, thereby preventing maceration. Certain perils are noted with its overuse, like occlusion of the sweat ducts progressing to form miliaria and also, accidental inhalation.

CARE OF SPECIAL AREAS

Diaper Area

The prevalence of diaper dermatitis is 4–15% in the neonatal period. The diaper area is quite susceptible to irritation and infection as it is a large, moist and occluded area. The various causes responsible for the dermatitis are moisture, occlusion, and irritants like soap, urine and feces. These factors increase the skin pH by activating enzymes like fecal proteases and lipases, break the skin barrier and affect its normal functioning. This also makes it more prone to infection with microorganisms such as *Candida albicans*, *Staphylococcus aureus*, and streptococci, leading to redness, scaling and even ulceration.

The diapers should be changed as frequently as possible, be the superabsorbent types (keep the area more dry) or the home ones. Luke warm water is sufficient to clean the area with the help of soft cotton balls. It is advisable to clean the bottoms from front to back. The skin is thoroughly air dried before putting on the next change. For sticky stools, one can use a mild soap. Twenty percent zinc oxide and petrolatum ointments are considered to be the treatment of choice in case an irritant diaper dermatitis occurs. Minimum use of diapers is encouraged when the rash occurs. Home diapers can be reused by simply washing in lukewarm water and then drying.

The customary methods and devices of cleansing have now been replaced by disposable infant wipes. These consist of an emulsion-type watery or oily lotion with both emollients and surfactants. They also contain additives, fragrances and preservatives. The wipes are considered to be mild on the skin and are as good or better than water or wash cloth. Newer advances have made diapers which directly transport petroleum to the skin, taking care of the dryness and irritation due to the diapers.

Scalp

Infantile seborrheic dermatitis occurs frequently in children less than 6 months of age. An emollient like coconut oil can be massaged onto the scalp and left overnight. This helps soften the crusts and aids in easy removal with a shampoo. A shampoo is basically a soap or synthetic detergent cleverly designed to clean the hair. It contains both cleansing and foaming agents. An ideal shampoo is one which is devoid of fragrances, preservatives and anti-inflammatory products and its pH is close to that of the tears, rendering it nonirritating to the child's eyes. A nonmedicated shampoo is sufficient to begin with, but if there is no improvement in the condition, medicated shampoos containing ketoconazole and zinc pyrithione may be used.

Other Areas

Umbilical cord care guidelines, issued by the World Health Organization include hand hygiene for the caregivers, using sterile tools to cut the cord, and using clean, sterile water and soap to wash the cord stump. Topical antimicrobials should be used only when unhygienic instruments are used to cut the cord. The nails of the newborns should be kept short and clean. Eyes should be cleaned very gently with the help of cotton balls immersed in boiled water.

SKIN INJURIES

Adhesive Injury

Adhesive dressings and tapes are used in the neonatal age group to fix the tubes and the monitoring machines in place. But, the repeated removal and reapplication of these dressing may lead to skin injuries, cause inconvenience, serve as a nidus for infection, and may also lead to hypopigmentation, atrophy and anetoderma.

Hence, adhesives should be used as minimally as possible. They should be left onto the skin for at least 24 hours before removal, and soft gauze wraps or foam strips should be used to fix the devices. The caregiver should gently remove the adhesive with the help of an emollient and warm water soaked cotton swab. Also, nonadhesive-based substances are available, but are not as effective, and are more expensive. One may use a liquid skin barrier or hydrocolloid dressing under the adhesives on the skin of the newborn to prevent peeling of the skin.

Thermal Injuries

Thermal burns may arise with prolonged use of a number of devices such as phototherapy lights, transcutaneous carbon dioxide monitoring, radiant warmers, and heating lamps and pads. The key to prevent them from occurring is proper monitoring, placing them at a correct distance, lowering the temperature, and reducing the exposure time.

Pressure Ulcers

The prevalence rate of pressure ulcers among newborns is 23%. It is due to the pressure exerted by devices like blood pressure cuffs, nasogastric and endotracheal tubes, arm boards, which collapse the immature arterioles and capillaries. Defective skin barrier, restricted mobility, insufficient nutrition all are important risk factors which predispose to the development of these ulcers.

The friction bearing sites such as nares, nasal septum, ears, occiput, knees, elbows, groin and thigh areas should be monitored as frequently as possible. It is advisable to keep the baby on water or air mattresses. The position of the newborn should be changed every 2 hours. Emollients may be applied to the flexural and friction bearing sites. Also, padding should be kept under equipment to avoid direct injury. Optimum care should be undertaken to prevent secondary infection and to provide adequate nutrition.

Wounds

The management of wounds comprises of wound culture and local antibiotic application such as mupirocin every 8–12 hours. The other supportive management includes wound irrigation with normal saline (diluted 1:1 with distilled water) and special dressing packages like hydrogels and hydrocolloid dressings. Wound debridement may be required rarely.

MORE ON THIS TOPIC

Adam R. Skin care of the diaper area. Pediatr Dermatol. 2008;25:427-33.

Blume-Peytavi U, Cork MJ, Faergemann J, et al. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. JEADV. 2009;23:751-9.

Blume-Peytavi U, Hauser M, Stamatas GN, et al. Skin care practices for newborns and infants: review of the clinical evidence for best practices. Pediatr Dermatol. 2012;29:1-14.

Darmstadt GL, Dinulos JG. Neonatal skin care. Pediatr Clin North Am. 2000;47:757-82.

Dyer JA. Newborn skin care. Semin Perinatol. 2013;37:3-7.

Fernandes JD, Machado MC, Oliveira ZN. Children and newborn skin care and prevention. An Bras Dermatol. 2011;86:102-10.

Heath SB, Narendran V, Visscher M. Role and biology of vernix. Neonatal Infant Nurs Rev. 2001;1:53-8.

Kuehl BL, Fyfe KS, Shear NH. Cutaneous cleansers. Skin Therapy. 2003;8:1-4.

Lawton S. Understanding skin care and skin barrier function in infants. Nurs Child Young People. 2013;25:28-33.

Lin RL, Tinkle LL, Janniger CK. Skin care of the healthy newborn. Cutis. 2005;75:25-30.

Ness MJ, Davis DM, Carey WA. Neonatal skin care: a concise review. Int J Dermatol. 2013;52:14-22.

Sarkar R, Basu S, Agrawal RK, Gupta P. Skin care for the newborn. Indian Pediatrics. 2010;47:593-8.

Chapter 48.3
Infections and Infestations
S Criton

BACTERIAL INFECTIONS

The bacteriae on skin may be grouped as commensals (those live harmlessly on the surface and within the follicles), transient dwellers (remains on the surface for a short period without multiplication), opportunistic pathogens (bacteria that are nonpathogenic usually, assumes the role of a pathogen and causes the disease under favorable circumstances) and pathogens (the bacteria always cause disease of the skin).

The natural defense of skin against bacterial infection is governed by a number of factors. These include the moisture content, the physical integrity of skin, the chemical factors, bacterial interference and production of antibacterial peptides. The pH of the skin, though considered an important factor of skin defense is proved wrong with recent studies. Common bacterial infections of the skin are listed in **Box 1**.

Etiology

The skin infection involves the complex interaction between the environment, host and pathogen. The immune status of the individual decides the gravity of the infection; so also the virulence of the organism. The common organisms causing skin infection are *Staphylococcus* and *Streptococcus*. They cause morphologically different manifestations of the skin such as impetigo, erysipelas, cellulitis, folliculitis, furuncle, carbuncle, ecthyma, blistering distal dactylitis, perianal infections and necrotizing fasciitis. In addition to the above-mentioned patterns, the bacteriae may elaborate various toxins in the body and cause diseases such as staphylococcal scalded skin syndrome (SSSS), streptococcal toxic shock syndrome and scarlet fever.

Impetigo

Impetigo is caused mainly by *Staphylococcus* and manifested as two distinct forms: nonbullous and bullous impetigo. *Nonbullous impetigo* starts as an erythematous papules, rapidly turns to vesicle, the vesicle ruptures and forms crust. The crust is classically described as *honey colored*. The lesions are mainly distributed over face and less commonly over limbs and trunk **(Fig. 1)**. Unless it is superinfected with streptococci, it may not have regional adenopathy. Impetigo is not commonly associated with constitutional features. In *bullous impetigo*, the lesion starts as a bullae and increase rapidly in size and remains on the skin for a few days and then ruptures. On rupture, a brownish, thin, flat crust is formed. In certain situations bullous impetigo starts healing from the center and results in circinate lesion. The lesion may usually

Figure 1 Impetigo

occur anywhere on the body. The usual complications of impetigo are SSSS and acute glomerulonephritis, if there is a coinfection with streptococci.

Treatment

The lesion should be thoroughly washed with soap and water. If it is heavily crusted, one may use either saline or potassium permanganate solution as compress. Depending on the severity of infection the choice of antibiotic varies between topical and systemic agents. If the infection is mild, topical antibiotic (fusidic acid, mupirocin) may suffice. Widespread or severe infections need the systemic erythromycin, ampicillin or cloxacillin.

Folliculitis and Furuncle

These are infections of the hair follicle caused by *Staphylococcus aureus*. The distinction between folliculitis and furuncle is based on the level of infection; if the infection is superficial, it is called as folliculitis, and deep infection is called furuncle. The level of demarcation of superficial and deep is based on the level of opening of sebaceous duct. If the infection is above the level of opening of sebaceous duct, it is called superficial and below, as deep. When many furuncles occur at a given time, it is called as furunculosis. Furunculosis is usually an indication of immunosuppression. The common conditions in which furuncle or furunculosis occur are diabetes mellitus and systemic corticosteroid treatment. Furuncle may develop in rapid succession in a given individual and persist for a long-time; this condition is called as recurrent furunculosis. This may be due to a carrier state in the index patient or in the contacts. It can also be due to methicillin-resistant *Staphylococcus aureus* (MRSA).

Clinical Features

Folliculitis presents as superficial pustule arising from the follicle. A hair is seen emerging through the pustule and it is surrounded by an erythematous rim. It may or may not be painful. At times, it may be pruritic. The common sites of involvement are the hairy region of the body. The furuncle presents as an erythematous nodule, which is painful and tender **(Fig. 2)**, usually over face, limbs and trunk. Furuncles usually occur in older children and adolescents.

Treatment

If the disease is limited, topical agents may suffice; if the infection is extensive systemic antibiotic (ampicillin, cloxacillin, or erythromycin) along with local measures is needed. The treatment

BOX 1 Common bacterial infections of skin
• Impetigo
• Erysipelas
• Cellulitis
• Folliculitis
• Furuncle
• Carbuncle
• Ecthyma
• Blistering distal dactylitis
• Perianal infections
• Necrotizing fasciitis.

Figure 2 Furuncle

Figure 3 Necrotizing fasciitis

of furuncle includes drainage of the content alone or addition of antibiotic as well. Local heat in the form of hot fomentation will help to reduce pain. The pus is drained by extracting the hair of affected follicle or a formal incision and drainage.

Ecthyma

Ecthyma is a superficial bacterial infection caused by both *Staphylococcus* and *Streptococcus* characterized by an ulcer covered with a slough. It starts as a small bullae or papule, which ruptures and forms an ulcer. The floor of ulcer contains *wash leather slough*. It is attached to the floor and difficult to remove. The treatment includes removal of slough either surgically or by use of compress. Usually surgical removal is required. Along with these an antibiotic such as ampicillin or cloxacillin is given.

Cellulitis and Erysipelas

Cellulitis is a spreading infection of the deep dermis and subcutaneous tissue commonly caused by streptococci. *Haemophilus influenzae* type B is considered an important cause of facial cellulitis in children. Rarely *S. aureus* may also be implicated in cellulitis. Cellulitis is characterized by erythema, rise in temperature, swelling, pain and tenderness. The edge of the lesion is indistinct and advances day by day. Along with these findings there will be constitutional features and regional adenopathy. If the infection is severe it may lead to bullae formation. If untreated, the affected area may become necrosed.

Erysipelas is an infection of dermis and has a well-defined raised border. The margins are raised. The affected area is erythematous and swollen. Vesicles are seen commonly over the lesion. It is not a common occurrence in children. It may involve the superficial subcutaneous tissue as well. Erysipelas is caused entirely by streptococci. In certain occasions the clinical features may be so indistinct and difficult to differentiate between erysipelas and cellulitis.

Treatment

Empirical treatment is initiated, based on the age of the patient, severity of infection and the immune status. The treatment of infant or child below 5 years of age should cover organisms such as *S. aureus*, *S. pyogenes*, and *S. pneumoniae*. The work-up should include blood culture. If the patient is less than 1 month of age, a lumbar puncture should also be done. In older children, if cellulitis occurs over extremities and is of mild severity, oral antibiotic is sufficient. If constitutional features are present and/or the patient

is immunosuppressed, parenteral treatment should be initiated. Erysipelas is treated with benzyl penicillin.

Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly spreading polymicrobial infection involving the subcutaneous fat and fascia, characterized by necrosis of skin and constitutional features. The risk factors include diabetes mellitus, immunosuppression, penetrating injury, renal failure; it can also occur in healthy individuals. The mortality ranges from 20% to 40%. The child presents with local swelling and constitutional features such as fever, headache, irritability and toxemia. The swelling rapidly increases and spreads to the surrounding skin. Along with this, color of skin changes from erythema to dusky red. There is extreme tenderness over the lesion. Within a short period, the skin becomes ischemic and necrosis sets in **(Fig. 3)**.

Early aggressive treatment helps to get a positive outcome. Surgical intervention helps to reduce the morbidity and mortality. All devitalized tissues are removed and fasciotomy performed. The excision should be sufficiently extensive to reach normal tissue. Intravenous penicillin G in high doses with intravenous metronidazole is administered. Alternatives include ampicillin/ sulbactam or piperacillin/tazobactam with clindamycin and ciprofloxacin.

Blistering Dactylitis

Blistering dactylitis is a superficial blistering infection common among school going children; occasionally it can occur in infants. It usually presents as a blister in an erythematous background over distal phalanx. The blister fluid is purulent. It may involve one or more fingers. The toes may also be involved. Usually the lesion is not painful. If untreated, the blister enlarges, and may extend to paronychial region. Herpetic whitlow is a close differential diagnosis. This condition usually involves the terminal phalanx, particularly at a site of damaged cuticle. Herpetic whitlow is usually painful. Blistering dactylitis is treated with penicillin, cloxacillin or cephalexin. In penicillin allergic patient erythromycin or clindamycin may be used.

Perianal Streptococcal Dermatitis

Perianal streptococcal dermatitis is a superficial form of *S. pyogenes* infection around anal orifice. Usually seen in children below 4 years; it may occur in the age group of 6 months to 10 years.

There is always a male predominance. Commonly it is associated with streptococcal pharyngitis. It presents with perianal itch, rectal pain or burning especially during defecation. As time passes by, there will be mucoid discharge and blood streaking of stools. Examination of perianal region will show erythema extending from anal orifice. The differential diagnosis of perianal dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse and inflammatory bowel disease. The treatment is with oral penicillin for 10 days.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome is caused by staphylococcal exotoxins A and B. From the focus of infection, the toxin diffuses and spreads hematogenously to distant parts of the body. The infective focus may be the nasopharynx or conjunctiva. In infants it may be umbilical cord. The focus need not be very evident. Renal prematurity and a genetic predisposition are suggested as etiological factors.

At the onset of the disease, the child becomes very irritable and resists handling. Along with this there will be a faint erythematous rash around orifices especially periorally and periorbitally as well as in flexors. Subsequently, the rash progresses to involve the entire face and trunk. Then the skin starts peeling off, leaving behind erosions and crusting **(Fig. 4)**. Examination will show an irritable child with tenderness of skin. Nikolsky sign is positive. There may be pharyngitis and conjunctivitis. There may be flexural accentuation. Radial crusting and fissuring are also seen around eyes and mouth. Intraoral lesions are usually absent. The severity of the disease is related to the toxin load in blood. The harmful effect is due to the absence or paucity of specific antitoxin antibody. These exfoliative toxins are serine proteases that produce a split in the granular layer. This split occurs due to binding and cleaving desmoglein-I within the desmosomes.

Differential Diagnosis

Diseases presenting with similar clinical picture include toxic epidermal necrolysis (TEN), drug eruption, pemphigus foliaceous and rarely epidermolysis bullosa. The important point of differentiation from TEN is the absence of oral mucosal involvement. To differentiate from pemphigus foliaceous, investigations such as skin biopsy and direct immunofluorescence study are required.

Treatment

Mainstay of treatment is supportive care and antibiotics. The antibiotic of choice is usually penicillinase resistant

Figure 4 Staphylococcal scalded skin syndrome

penicillin. Clindamycin is also suggested as an effective drug. Local compresses will help to remove crusts and expedite healing. Adequate fluid and electrolytes should be maintained. Corticosteroids should be avoided.

The outcome is usually good. The skin heals without scarring. Mortality is rare and if occurs, it is due to sepsis.

Staphylococcal Toxic Shock Syndrome

Toxic shock syndrome (TSS) is a toxin-mediated disease produced by staphylococcal exotoxin as well as enterotoxin. It is characterized by fever, erythroderma, shock and multisystem involvement. There are two types of TSS such as menstrual and nonmenstrual. The menstrual TSS is caused by exotoxin. TSST-1, produced by *S. aureus*. It is commonly associated with tampon use whereas non-menstrual TSS is caused by enterotoxin and associated with various clinical situations such as influenza, sinusitis, burn wounds and postpartum period. The nonmenstrual TSS has a tendency to recur.

Toxic shock syndrome is due to infection or colonization of *S. aureus*. These *S. aureus* produce TSST-1. The absence of antibodies against TSST-1 forms an important risk factor. This toxin acts as a superantigen and causes massive liberation of cytokines and chemokines as well as clonal T-cell expansion. This in turn causes all the clinical manifestation. Other risk factors are described in Chapter 29.11 on staphylococcal infections.

Clinical Features

Both the types have similar presentation. The onset is abrupt characterized by fever and diffuse rash. There may be flexural accentuation. It is associated with shock and multiorgan involvement. The eruption of TSS is characteristically termed as *diffuse macular erythroderma*. As the disease advances there will be peripheral edema, hyperemia of conjunctiva and mucous membrane as well as strawberry tongue. This may cause some confusion with Kawasaki disease. The absence of thrombocytosis and lymphadenopathy are distinguishing features. Multiple organs may be involved which include cardiovascular, hepatic, gastrointestinal and central nervous system. Diagnostic criteria are listed in Chapter 29.11. The differential diagnosis of TSS includes scarlet fever, Kawasaki disease, SSSS, atypical measles, other viral exanthems and drug reactions.

The treatment involves meticulous supportive care, management of multiorgan failure, identification and drainage of infection and early institution of antibiotics. The recommended antibiotics are beta-lactamase resistant antibiotics such as oxacillin and/or first or second generation cephalosporins. Vancomycin should be the antibiotic of choice for MRSA. Intravenous immunoglobulin (IVIG) may be considered if there is inadequate response to treatment for a reasonable period.

SUPERFICIAL FUNGAL INFECTIONS

The superficial fungal infections involve the skin, its appendages and mucous membrane, and are caused by dermatophytes, yeasts and molds.

Dermatophyte Infections

Dermatophyte infections are mainly caused by three genera of fungi such as *Microsporum, Trichophyton* and *Epidermophyton*. Depending on the site of infection of skin, the clinical manifestations vary and named accordingly: fungal infection of scalp (Tinea capitis), body (Tinea corporis), groin (Tinea cruris), axillae (Tinea axillaris), face (Tinea faciei), beard area (Tinea barbae), hand (Tinea manuum), foot (Tinea pedis) and nails (onychomycosis). The clinical features depend on the infectious agent, body site and the immune status of host.

Tinea Corporis

The typical lesion may be described as an annular or polycyclic lesion with peripheral rim of activity and central clearing **(Fig. 5)**. The signs of activity include erythema, papule, pustule, vesicle and scaling. Children of all ages may be involved. The child is brought because of asymptomatic lesion alone or may be due to pruritic lesion.

Tinea Cruris

Tinea cruris is usually seen in adolescent children. It extends from groin both upwards and downwards through the medial aspect of thigh. The periphery is active with erythematous raised border and central clearing. The infection may spread to the perineum and buttocks.

Tinea Capitis

Dermatophyte infection of scalp is usually seen in children. On the scalp, the fungal infection may be named as black dot fungus, gray patch fungus, kerion **(Fig. 6)** and fauves. It primarily presents as loss of hair, scaling of scalp. In black dot fungus, the hair is broken at the level of scalp and appears as black dots on the scalp in a circumscribed area **(Fig. 7)**. In gray patch, the hair is broken at different lengths and the scalp will be scaly. In kerion, the affected scalp appears as boggy swelling with crusting and pustules with loose hairs. There will be regional adenopathy, which may be tender also.

The favus usually develops in immunocompromised or malnourished individual. The typical lesion is cup-shaped structure known as scutula on the affected area. There will be crusting and scaling along with these structures.

Tinea manuum, Tinea pedis and onychomycosis are not very common among children.

The diagnosis of dermatophyte infection is by clinical features, demonstration of fungi in potassium hydroxide preparation and rarely by culture.

The treatment of dermatophyte infection is by both topical and systemic antifungals. If the disease is of one or two lesions, topical antifungals will suffice. The indications for systemic antifungals include extensive involvement, failure of topical, inappropriate therapy with topical steroid and immunocompromised individuals. The scalp infections especially kerion and favus are treated with systemic antifungals. For scalp infection, griseofulvin is considered the drug of choice. Recently, terbinafine is also recommended. The duration of treatment may be prolonged such as 4–6 weeks.

Tinea Incognito

Tinea incognito is a dermatophyte infection modified with application of topical steroids. This is minimal or absent inflammation; however, the border of the lesion will be clear cut. The polycyclic nature of the border will help in the diagnosis **(Fig. 8)**. The scraping for fungus may be negative. High index of suspicion will help in the diagnosis. The treatment is with systemic antifungals such as terbinafine for sufficiently longer period such as 3–4 weeks.

Malassezia Infection

Malassezia is a dimorphic lipophilic fungus which resides as a normal commensal of skin of humans and under appropriate circumstances transform into hyphal forms and causes disease. It causes Pityriasis versicolor. In children it is seen mainly over face and trunk, and is one of the important differential diagnosis of hypopigmented patch on the face.

Clinical Features

The disease presents as well defined hypopigmented or hyperpigmented patch over face, trunk and flexors. Usually the margins are irregular **(Fig. 9)**; however, it may assume any morphology. One characteristic feature of the lesion of pityriasis

Figure 6 Kerion

Figure 5 Tinea corporis

Figure 7 Black dot fungus

Figure 8 Tinea incognito

Figure 9 Pityriasis versicolor

versicolor is that the appearance of the normal skin within the lesion as if the invasion of normal skin into the lesion. The size of the lesion is variable from very small to large. The color may vary from hypopigmentation to hyperpigmentation, and hence the name versicolor. The hyperpigmentation may be brownish to darkly pigmented. The surface is scaly and typically described as *powdery* or *furfuraceous*. Usually it is asymptomatic but may be pruritic. The pruritus may be more while sweating.

The *diagnosis* is made by clinical appearance and by demonstration of fungus in potassium hydroxide preparation of scrapings. Under microscope, the classical appearance of *meat ball and spaghetti* help to make the diagnosis.

The *differential diagnosis* may vary with site of involvement. On the face, Pityriasis alba is an important differential diagnosis. The others may be indeterminate leprosy, early vitiligo, nutritional dyschromia and postinflammatory hypopigmentation. Nowadays topical steroid therapy forms an important differential diagnosis as it causes hypopigmentation over the trunk. Leprosy, hypopigmented mycosis fungoides, postinflammatory hypopigmentation are the other common differential diagnoses.

The *treatment* is usually with topical agents. The usual drugs used are clotrimazole, miconazole, ketoconazole, and sertaconazole. The systemic drugs used are fluconazole and itraconazole. The systemic use of ketoconazole is not advisable. The usual practice is the use of ketoconazole shampoo over the affected area for about 15 min before bath followed by thorough wash for 3–4 weeks daily.

Candidal Infections

Candidiasis is another common yeast infection of children and adults. Children of all ages are affected by this fungus. Candidiasis affects the skin and mucous membrane. Commonly the intertriginous area of skin is affected; while the oral and genital mucosas are the mucosal sites. Apart from these sites, the nail folds (candidal paronychia) and even nails (candidal onychomycosis) are the other sites of involvement. Candidiasis is described in detail in Section 33 in a separate chapter.

PARASITIC INFESTATIONS

Human skin can be infested by several parasites. Identification of the causative agent helps to treat these diseases effectively. The lice and scabies infestation are important in children.
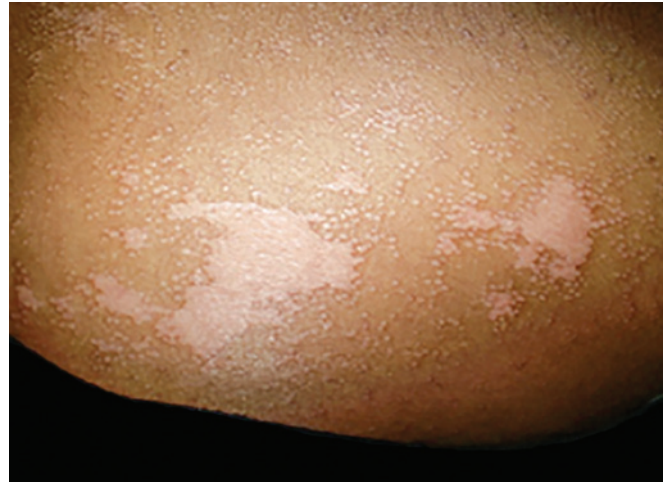
Pediculosis

Pediculosis is one of the common problems of childhood worldwide. It is caused by lice of the order Phthiraptera. They are wingless, dorsoventrally flattened insects. Humans are parasitized by three different species: *Pediculus capitis* (the head louse), *Pediculus humanus* (the body louse) and Pthirus pubis (the public louse or crab louse).

Pediculosis Capitis

Pediculosis capitis or the head louse infestation is the disease of scalp in school going children. Girls are affected more. Transmission is primarily by head-to-head contact. In transmission, the role of fomites such as combs, hat, etc., is controversial.

The female louse cements its eggs to the hair shaft close to scalp. The eggs are oval and with an operculum. After about 6–8 days, the egg hatches and nymph comes out. The empty egg remains attached to hair and is known as nits **(Fig. 10)**. The nymph attains maturity after three moults in 8–10 days. The female adult becomes gravid in 24 hours and lays eggs in 6–10 days. The life span of adult louse is 17–28 days.

Clinical features The presence of louse is not felt initially. As days pass by sensitization to saliva and fecal material occurs and this

Figure 10 Nits

results in pruritus of scalp. Pruritus leads to excoriation. At times secondary infection occurs, leading to impetigo of scalp. In certain cases pruritic papules occur in the nape of neck and back of upper chest. Presence of nits is also a sign of pediculosis. Sometimes the hair may be matted together (plica). The diagnosis of active infestation is by demonstration of active lice. Sometimes psoriasis and hair casts may be mistaken for pediculosis capitis.

Treatment The effective treatment of pediculosis capitis is with the use of pediculicide followed by manual nit removal (nit picking). A number of drugs are used as pediculicide such as lindane 1% (gamma benzene hexachloride), pyrethrins (natural plant extract) permethrin (a synthetic pyrethroid), malathion (organophosphate), ivermectin, carbaryl and co-trimoxazole. Alternative products with variable efficiency are also used to kill the louse such as petroleum jelly, hair pomade, olive oil, benzyl alcohol lotion, dimethicone and spinosad. Gamma benzene hexachloride, permethrin and topical ivermectin are preferred drugs.

The pediculicides are applied for 6–8 hours and then washed off; a second application after 8–10 days is mandatory as these drugs are not ovicidal. Along with the application, antihistamine should also be given to control itching and should be continued for minimum of 2 weeks as the itching will persist even after the death of pediculi. The treatment with pediculicide should be followed by manual removal of nits.

Pediculosis Corporis

Pediculosis corporis is caused by *Pediculus humanus*. Morphologically the louse is similar to head louse but larger in size. It lives in clothing and goes to the body only for feeding. Pediculosis corporis is seen commonly among poor and thrives well in overcrowded, unhygienic situations. The clothing louse is the vector of typhus, trench fever and louse-borne trench fever.

Clinical features Itching is the common complaint of the infected. There will be excoriation marks; along with this there may be evidence of secondary bacterial infection. If pediculosis corporis is present for a long-time the body become hyperpigmented. This is known as *vagabond* disease. Clothes should be examined for the lice and eggs.

Treatment Treatment of pediculosis corporis should be directed towards clothing of the individual. The cloth should be properly cleaned. Any means of applying uniform heat, wet or dry at a temperature of 65°C (149° F) for 15–30 min is sufficient to kill all lice and their eggs. If it is not possible to clean, the clothing should be burned. Following appropriate care of clothing, the patient is treated with pediculicide from head to toe for 8–14 hours and repeated in 1 week for killing of newly hatched pediculi.

Pediculosis Pubis

Pediculosis pubis is caused by *Pthirus pubis*. This is commonly seen in adolescent boys. The commonly affected sites include pubic and perianal areas. Occasionally, the pubic lice may be seen in mustache, beard, axillae, eye-lashes or scalp hair. The most common mode of transmission is intimate body contact as in sexual activity. The other modes being infected clothing, towels or beds. Children usually acquire the louse by sharing a bed or towel with an infested family member. In children, it may also be seen on eyelashes. The treatment includes use of gamma benzene hexachloride, permethrin and oral ivermectin. A second treatment after 1 week is also recommended to kill the hatching new ones.

Scabies

The human scabies is caused by the mite, Sarcoptes *scabiei* var hominis and characterized by pruritic papules occurring in the web space of fingers, ulnar border of wrist, axillary folds, around the umbilicus, external genitalia of males and around the areola of females. It affects all ages, sexes, races and nationalities equally.

Sarcoptes scabiei var hominis is host specific. The female gravid mite burrows the skin and as they burrow lays eggs. These hatch within 2–3 days to produce a larva. The larva crawls over the skin and after three moults reaches adulthood. The completion occurs in the burrow of skin. The life span of female mite is 4–6 weeks.

Scabies is transmitted by close contact. Infants and young children are particularly likely to transmit infestation as there is increased chance of close contact. The fomites are also implicated in the transmission, though the evidence is not very strong.

Clinical Features

The patients present with pruritus of varying intensity. It is more during night. The classical lesion of scabies is a burrow. The burrows are usually seen in the web spaces of fingers. In infants burrows may be seen in palms and soles as well as sides of feet. Burrows may be demonstrated by application of ink on the surface of skin for some time. The ink enters the burrows by capillary action and may be visualized after wiping it off. In addition to the burrows, papules, excoriations, nodules **(Fig. 11)**, vesiculopustules, eczematization and crusted lesions are also seen. The lesions are distributed mainly over the hands, web spaces, ulnar aspect of wrist, axillary folds, scrotum and shaft of penis, around umbilicus and around areola. In older children the face, hands and feet are spared.

Infantile Scabies

The scabies in infants is different clinically from that of adults and older children. The lesions in infant are more inflammatory and there is abundance of pustules **(Fig. 12)**. In addition to the usual sites of involvement, palms, soles, scalp, face and area around oral orifice may also be involved. The demonstration of burrows is easier in infants.

Crusted Scabies (Norwegian Scabies)

This type of scabies is different from other types in having innumerable mites on the affected patient and the lesions are

Figure 11 Nodular scabies

Figure 12 Infantile scabies

Figure 13 Eczema herpeticum

hyperkeratotic and scaly. It may be mistaken for psoriasis. This variant usually occurs in immunocompromised, Down syndrome, HIV infected and organ transplant recipients.

Treatment

Topical preparations of gamma benzene hexachloride, permethrin, sulfur, crotamiton 10% and benzyl benzoate are used for treatment. Gamma benzene hexachloride is contraindicated in children below 2 years and in those with pre-existing CNS disease for fear of neurotoxicity. Permethrin 5% cream is considered as the treatment of choice in children. If there is secondary infection, it should be treated first and then antiscabetic treatment is initiated. Along with the treatment, antihistamine is given and should be continued for 2 weeks as the pruritus will persist for about 2 weeks of treatment.

The following procedure is to be followed in the treatment of scabies. The child should be given a thorough scrub bath. Then the drug is applied from neck downwards sparing no areas. It should be kept on the body for 24 hours. If it is washed off in between, the drug must be reapplied. All the family members are treated irrespective whether they are having itch or not. The fomites are appropriately treated with washing. After about 7–10 days, the drug must be reapplied in the same manner. This will complete the treatment of scabies by topical agent.

Systemic drug, ivermectin 200 mcg/kg single oral dose, is also advocated in the treatment of scabies. It causes neuroparalysis of the mite. It should be repeated after 8–10 days.

VIRAL DISEASES

Herpes simplex virus type 1 is primarily associated with oral and labial grouped vesicular lesion. According to the site of involvement, the disease may be named as herpetic gingivostomatitis, ocular herpetic infection, herpes labialis, cutaneous herpes infection and herpes genitalis. Most of these conditions have been already discussed in the Section 32 on chapter on Herpes Infections.

VIRAL INFECTIONS

Eczema Herpeticum

Eczema herpeticum (EH) or Kaposi's varicelliform eruption is a severe disseminated HSV infection that occurs in individuals with atopic dermatitis and other chronic skin disease such as pemphigus, exfoliative dermatitis, etc. There is an abrupt onset of vesicles, vesiculo pustules over already affected areas of skin

(Fig. 13). This is followed by constitutional features such as fever, irritability, lethargy, etc. Eczema herpeticum usually occurs in young children and infants. The treatment is by parenteral acyclovir in severe cases. In mild cases, oral therapy is sufficient.

Verruca Vulgaris

Verruca vulgaris or warts are caused by human papilloma virus types 1, 2, 4 and 7. These transmitted by autoinoculation, heteroinoculation (through fomites), iatrogenically, and by vertical and sexual transmission. Depending on the morphology of the lesion and sites of involvement, the warts named as digitate warts, plane warts, periungual and subungual warts, palmar warts, plantar warts, mosaic warts and anogenital warts.

The common warts are dome-shaped papules with verrucous surface. They are seen mainly over the dorsal surface of hands, around the nails (periungual warts), beneath the nails (subungual warts), soles of feet (plantar wart) as well as palmar surface (palmar wart). Digitate warts are long with narrow peduncles. Plane warts are flat topped with smooth surface. These warts are also seen commonly over face and neck. Koebnerization is common among these warts. Plantar warts are seen singly or may coalesce together and result in mosaic warts. The single plantar warts are endophytic and may be seen in pressure points. It may be differentiated from the *corns*. The differentiation is made by applying pressure over the lesion; if there is pain on application of lateral pressure, the lesion is more likely to be wart. If pain is felt on application of perpendicular pressure, the lesion is probably corn. Thrombosed capillaries may be seen in case of plantar warts.

Treatment

The choice of treatment depends on location of wart, pain threshold of the patient, number, immune status, comorbid condition, preferences of patients and physician, and availability of instruments. The medical treatments consists of application of salicylic acid, combination of salicylic acid and lactic acid, antivirals such as imiquimod, cidofovir, 5 fluorouracil, injection of interferon α, local vaccination with intralesional injection of mumps and *Candida* antigen. Surgical measures include surgical excision, electric, cryosurgery and thermal cautery. Laser treatment and photodynamic therapy are also useful.

Anogenital Warts (Condylomata Acuminata)

Anogenital warts are primarily associated with HPV types 6 and 11. It may also be associated with types 16, 18 and 30. The

Figure 15 Molluscum conjunctivitis

Figure 14 Molluscum contagiosum

lesions are seen in the anogenital area. A child diagnosed as having anogenital was should be thoroughly evaluated to rule out sexual abuse. It is one of the common sexually transmitted infections. However, other modes of spread such as vertical, autoinoculation, heteroinoculation as well as through fomites are also possible. The lesions are skin-colored or flesh-colored papules seen over the shaft of penis, glans, scrotum and vulva as well as around anal orifice. Sometimes, intravaginal and cervical lesions are also seen.

Treatment

The commonly used drug is application of podophyllum extract over the lesions. Application of imiquimod is also useful in anogenital warts. Occasionally cryotherapy, laser therapy and surgical ablation are also utilized.

Molluscum Contagiosum

Molluscum contagiosum (MC) is caused by a DNA virus of the *Molluscipox* genus. It can occur at any age. The transmission is through skin to skin contact, fomites or by autoinoculation. There is an increased incidence of MC in children who frequent swimming pools.

Clinical Features

The lesion is a skin colored papule with central umbilication **(Fig. 14)**. In immunocompetent individuals, the size varies from 1 mm–10 mm. In immunosuppressed individuals, the lesion is larger and known as *giant molluscum contagiosum*. The lesions may be seen in any part of the body. Axillae, sides of neck, face, lower abdomen and thighs are the preferred sites. The number of lesions

is limited but in immunosuppressed there may be innumerable number. Large number of lesions is also seen in children with atopic dermatitis. In about 10% of cases, there may be perilesional dermatitis and it is known as *molluscum dermatitis*. This dermatitis settles with the disappearance of molluscum lesion. Molluscum along with the lid margin may cause conjunctivitis and is known as *molluscum conjunctivitis* **(Fig. 15)**.

Treatment

Mild infections may resolve spontaneously. However, there is a risk of spread and hence it is better to treat the disease at the earliest. Modalities used in the treatment include topical application of phenol, salicylic acid, lactic acid, salicylic acid with lactic acid, electrocautery, cryocautery, laser treatment, cantharidin, and 10% potassium hydroxide.

MORE ON THIS TOPIC

Hatipoglu N, Hatipoglu H. Combination antifungal therapy for invasive fungal infections in children and adults. Expert Rev Anti Infect Ther. 2013;11:523-35.

Hawkins DM, Smidt AC. Superficial fungal infections in children. Pediatr Clin North Am. 2014;61:443-55.

Larru B, Gerber JS. Cutaneous bacterial infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* in infants and children. Pediatr Clin North Am. 2014;61:457-78.

Mazzone L, Schiestl C. Management of septic skin necroses. Eur J Pediatr Surg. 2013;23:349-58.

Sanders JE, Garcia SE. Pediatric herpes simplex virus infections: an evidence-based approach to treatment. Pediatr Emerg Med Pract. 2014;11:1-19.

van Onselen J. Skin infections in children. Part 1. J Fam Health Care. 2013;23:19-22.

Chapter 48.4
Congenital Vascular and Melanocytic Malformations
Manish K Shah

Congenital malformations are benign overgrowths which are present at birth or appear shortly after birth, usually in the 1st month. These are listed in **Box 1**. The more common vascular and melanocytic birthmarks are described.

NEVUS SIMPLEX (SALMON PATCH)

These are the most common vascular lesions of infancy. They occur as pink flat lesions on the forehead, eyelids or nape of the neck. These usually fade within the first 1–2 years of life. Lesions on the neck may be more persistent.

INFANTILE HEMANGIOMA

Infantile hemangioma (IH) is the most common benign soft tissue tumor of childhood. IH has a distinctive clinical course. They are usually not present at birth or occur as precursor lesions like areas of pallor or telangiectasia. Over the first few weeks, they become prominent followed by a phase of exponential growth until 9–12 months of age. This culminates into a phase of involution that may last 6–10 years. Some IH resolves completely whereas others leave behind residual changes like telangiectasia, scarring or fibrofatty tissue. The most common complications of IH are ulceration, visual compromise, auditory canal obstruction and cardiac compromise. Ulceration usually occurs during the proliferative phase and can be very painful.

Infantile hemangioma can occur as superficial, deep or mixed lesions. Superficial IH are red-lobulated variably-sized raised lesions **(Fig. 1)**. Deep IH presents as subcutaneous nodules and tumors with a bluish hue. Mixed IH has a superficial and deep component.

Treatment

Since IH can bleed if scratched, fingernails should be kept short. If bleeding occurs, patients are instructed to apply pressure with a clean cloth and report to the closest casualty department. Given that IH regresses eventually, in most cases parents are reassured with instructions for regular monitoring. Early and decisive intervention is warranted if the hemangioma is situated near the eyes or on lips, tip of the nose, anogenital region. Segmental hemangiomas and extensive highly proliferating hemangiomas also need immediate intervention. IH showing complications, especially early ulceration and presence of multiple IH (> 5 IH have increased risk of visceral IH) also need early treatment. In multiple IH, ultrasound abdomen is advisable since the liver is most commonly affected. The airway, heart and brain are less commonly involved.

Oral β-blockers

These have become first-line therapy for proliferating IH. Propranolol 2 mg/kg/day in divided doses is preferred. The duration of treatment ranges from 6 months to 12 months. Propranolol ideally should be given till the child reaches 1 year of age (usually the end of the proliferating phase) in order to prevent rebound regrowth. Typically, the color becomes lighter and the IH softer within 24–48 hours of propranolol therapy. Common adverse effects of propranolol include bradycardia, hypotension, sleep disruption, acrocyanosis and diarrhea. Most importantly, a watch needs to be kept for hypoglycemia that can be fatal.

BOX 1 Congenital cutaneous malformations

Common vascular malformations
- Nevus simplex
- Infantile hemangioma
- Capillary malformation

Comparatively rarer malformations
- Congenital hemangiomas
- Vascular malformations (venous, glomuvenous, lymphatic, arterio-venous, combined)
- Tufted angioma (with or without Kasabach-Merritt syndrome), Kaposiform hemangioendothelioma (with or without Kasabach-Merritt syndrome) and spindle cell hemangioendothelioma
- Dermatologic-acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma)

Common melanocytic malformations
- Congenital melanocytic nevus
- Café-au-lait macule
- Mongolian spot

Combined vascular and melanocytic malformations
- Phakomatosis pigmentovascularis.

Oral Corticosteroids

High dose prednisolone 2–3 mg/kg/day tapered off gradually over months was hitherto used for rapidly proliferating IH. Steroids diminish proliferation as against β-blockers that shrink IH. Due to this and adverse effects, oral corticosteroids are no longer preferred therapy for IH.

Lasers

Pulsed dye lasers are now used only in ulcerated IH to hasten re-epithelialization and ease pain.

Topical β-blockers

Recently, topical timolol solution has been used safely and effectively for small and superficial IH. Due to concerns of systemic absorption, dose should not exceed 1–2 drops of timolol twice daily.

Treatment of Ulcerated Infantile Hemangioma

Ulceration is a complication that can occur in proliferating IH. Tissue breakdown can be complicated by bleeding, secondary infection, pain and possibly permanent scarring. Local wound care includes saline compresses, topical antibiotics and nonsticking

Figure 1 Infantile hemangioma

dressings like paraffin-embedded gauze. Oral antibiotics and analgesics may be required.

CAPILLARY MALFORMATION (PORT-WINE STAIN, NEVUS FLAMMEUS)

Capillary malformations (CMs) are flat vascular lesions **(Fig. 2)** and the most common malformations. Malformations are present since birth and grow darker very slowly as age increases (compare with IH). As adolescence approaches, CMs may become thicker and develop secondary vascular blebs that resemble granuloma pyogenicum **(Fig. 3)**. Treatment of CM is primarily for aesthetic reasons. Multiple sessions of vascular lasers can fade CMs. Face, neck and chest lesions respond better than limb lesions.

Syndromes Associated with Capillary Malformation

Sturge-Weber Syndrome

It is characterized by CM in V1 (ophthalmic) distribution of the trigeminal nerve, leptomeningeal angiomatosis (mainly presenting as seizures) and glaucoma. Multidermatomal and bilateral CM on face have a higher risk of central nervous system (CNS) involvement. CM in the V1 distribution portend the maximum risk of CNS and/or eye complications, the risk being much higher, if the CM involves the entire V1 region. Magnetic resonance imaging (MRI) can pick-up cerebral atrophy, enlargement of choroid plexus and venous abnormalities. The classical cortical *tram-line* calcifications are better identified by computed tomography (CT) scan.

Klippel-Trenaunay Syndrome

It manifests with vascular malformation (most often CM), venous varicosity and hyperplasia of soft tissue and bone. Lower extremities are most frequently affected. If there is associated arteriovenous malformation, it is termed Parkes-Weber syndrome.

CONGENITAL HEMANGIOMAS

The salient features and differentiating features from IH and vascular formations are summarized in **Table 1**.

Figure 2 Capillary malformation

Figure 3 Capillary malformation with secondary vascular growths

Table 1 Differentiating features of common cutaneous malformations

	Infantile hemangioma	*Congenital hemangioma*	*Vascular malformations*
Nature of vascular lesion	Proliferating embryonal tumors that probably stem from placental tissue or resemble it	Congenital vascular tumors distinct from IH	Localized, structural irregularities of the vasculature which occur due to developmental defects during vasculogenesis
Appearance at birth	Absent at birth; 50% of cases show precursor lesions like telangiectasia or erythematous macules	Erythematous or bluish plaques or firm nodules	Present since birth. Appearance depends upon type of vascular malformation
Types		Types: • RICH • NICH • *Tufted* angioma • Kaposiform hemangioendothelioma	• Venous • Lymphatic • Arterial • Arteriovenous • Capillary • Mixed
Growth pattern	Initial growth for 6–9 months followed by a phase of stabilization. Slow involution then occurs, sometimes completely, by the age of 4–6 years of age	• *RICH:* Regression begins within few days of birth. Regression completes within 3 months • *NICH:* Progressive growth, increased by infections	Steady growth commensurate with rest of body
Complications	• Ulceration • Excess growth • Associated defects • Feeding difficulties	• Rapid growth (except for RICH) Infection • Bleeding • Kasabach-Merritt syndrome	• Associated defects • Visual obstruction

Abbreviations: IH, infantile hemangioma; RICH, rapidly involuting congenital hemangioma; NICH, noninvoluting congenital hemangioma.

KASABACH-MERRITT SYNDROME

Kasabach-Merritt syndrome (KMS) is a catastrophic event that can occur in vascular tumors, mainly tufted angiomas and kaposiform hemangioendotheliomas. By and large, KMS does not occur in IH. KMS is a triad of thrombocytopenia (due to platelet trapping), coagulopathy and microangiopathic hemolytic anemia.

CONGENITAL MELANOCYTIC NEVUS

Congenital melanocytic nevus (CMN) is a melanocytic lesion that is typically present since birth. CMN is classified according to their greatest diameter in adulthood. They are defined as small (<1.5 cm), medium (1.5–19.9 cm) or large (>20 cm). Large congenital melanocytic nevi have an increased risk of malignant melanoma (0.7–2.9%). Large and giant CMN on the head, neck and back may be associated with neurocutaneous melanosis, where nevus cells proliferate in the leptomeninges. Neurocutaneous melanocytosis can present within the first 3 years of life with lethargy, headache, irritability, recurrent vomiting, convulsions, bulging anterior fontanel, photophobia, papilledema and neck stiffness. Even in the absence of symptoms, MRI can pick-up focal areas of high signal on T1-weighted images in one or more areas of the brain.

Congenital melanocytic nevus presents as brown or black papules, nodules or plaques. Larger CMN often has a thickened, warty surface along with hypertrichosis. Variations in color, nodularity, erosions and ulcerations in giant CMN may occur and do not always signal malignant transformation. In addition to melanomas, other soft tissue sarcomas too have been described in CMN.

Surgical intervention for CMN is controversial and not proven to reduce malignant risk or improve quality of life.

MORE ON THIS TOPIC

Arad E, Zuker M. The shifting paradigm in the management of giant melanocytic nevi: review and clinical applications. Plast Reconstr Surg. 2014;133:367-76.

Garzon MC, Huang JT, Enjolras O, et al. Vascular malformations: Part I. J Am Acad Dermatol. 2007;56:353-69.

Maguiness SM, Liang MG. Management of capillary malformations. Clin Plast Surg. 2011;38:65-73.

Marqueling AL, Oza V, Frieden IJ, Puttgen KB, et al. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol. 2013;30:182-91.

Püttgen KB. Diagnosis and management of infantile hemangiomas. Pediatr Clin North Am. 2014;61:383-402.

Chapter 48.5
Vitiligo and Other Hypopigmentary Diseases

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Different skin colors result from differences in the size and number of melanosomes and not necessarily the number or density of melanocytes. Disorders of pigmentation can result from migration abnormalities of melanocytes/melanoblasts from the neural crest to the skin during embryogenesis, impairment of melanosome transfer to surrounding keratinocytes, alterations in melanin synthesis, defective degradation or removal of melanin, or immunologic or toxic mediated destructions of melanocytes. These mechanisms are controlled by several genes.

Hypopigmentation refers to any form of decreased pigmentation, whereas *hypomelanosis* is specifically a decrease in melanin content. *Depigmentation* is total loss of skin color, most commonly due to disappearance of preexisting melanin pigmentation, as in vitiligo.

DIAGNOSIS OF HYPOPIGMENTATION

Any child with hypopigmented lesions should be examined under both visible and UVA light [i.e., ~365 nm (Wood lamp)]. This is especially useful in circumscribed lesions, individuals with skin types I or II and neonates. Most of these conditions are diagnosed clinically. Histologic examination is helpful for hypomelanosis associated with inflammatory processes (e.g., sarcoidosis, leprosy, mycoses fungoides). Quantification of the melanocyte density by incubation of biopsy specimens with dihydroxyphenylalanine (DOPA; detects melanocytes with tyrosinase activity) or melanocyte-specific immunohistochemical stains such as Mel-5 and Melan-A/MART-1 and ultrastructural studies are performed primarily for research purposes.

EARLY ONSET HYPOPIGMENTATION

Most of these disorders present at birth or during first 2 years of life have a genetic basis. Clinically, these disorders can be divided into those characterized by generalized hypopigmentation and those causing localized disease.

Generalized Hypopigmentary Disorders

These disorders occur due to mutations of genes responsible for the melanin production or processing of melanosomes. During embryogenesis, progenitor melanoblasts migrate between mesodermal and ectodermal layers to reach their final destinations in the epidermis and hair follicular bulbs as well as the inner ear cochlea, choroids, ciliary body and iris. Therefore, in addition to the skin and hair, the eyes can also exhibit pigmentary dilution and there can be associated hearing impairment. Although the number of melanocytes can be normal, there is a reduced melanin production or a reduced transport and/or transfer of melanosomes to the keratinocytes. Wood's lamp examination exhibits hypopigmentation rather than depigmentation. Various possible mechanisms have been proposed to explain the reduced melanogenesis:

- Absence of tyrosinase activity: Oculocutaneous albinism type 1A (OCA-1A)
- Reduced tyrosinase activity: Oculocutaneous albinism type 1B (OCA-1B)
- Impaired tyrosinase function: Metabolic disorders or nutritional deficiencies (copper, selenium or phenylalanine hydroxylase).

Albinism

Two different types of albinism have been identified: (i) ocular albinism (OA) and (ii) OCA albinism. In OCA, the ocular manifestations like nystagmus, photophobia and iris translucency are often the first clue leading to the diagnosis. The ocular abnormalities are due to misrouting of the optic nerve. Tyrosine hydroxylase is important in the proper routing of retinal projections at the optic chiasm during development. OCA is divided into four subtypes with a wide variation in color of hair and skin, ranging from a complete absence of pigment (OCA-1A) to subtle pigmentary dilution (OCA-1B). In OCA type 1A, there is complete absence of tyrosinase activity, leading to permanent and complete absence of pigment from birth. In OCA types 1B, A2, A3 and A4, the pigment production may increase over time. The pigmentary dilution may be subtle in OCA-1B, 2, 3 and 4 along with Hermansky-Pudlak and Chediak-Higashi syndromes and comparison with family members is often helpful.

Management Genetic counseling to specify the subtype of OCA for prognosis and evolution as well as the consequences in case of later pregnancy. Besides a stringent ophthalmologic follow-up, dermatological care should focus on the screening and prevention of development of malignant lesions, sun protection and camouflage.

Other Associated Syndromes

Children with diffuse hypomelanosis should undergo a systemic evaluation to exclude other rare disorders **(Table 1)**. Hermansky-Pudlak syndrome can be suspected if there are signs of an associated platelet dysfunction: repeated episodes of epistaxis, abnormal development of bruise. Griscelli, Elejalde and Chediak-Higashi syndromes have been termed as *silvery hair syndromes* **(Fig. 1)**. Impairment of melanin synthesis occurs in certain diseases of inborn errors of metabolism, such as phenylketonuria, homocystinuria and histidinemia, which are due to the absence or defect in phenylalanine hydroxylase, cystathionine β synthase and histidase, respectively. *Menkes syndrome* is an X-linked recessive disorder due to inappropriate intracellular copper storage. Pigmentary abnormalities consist of lightly pigmented hair and generalized or localized hypopigmentation. Progressive central nervous system deterioration occurs and results in death by 3 years of age. Pigmentary dilution and skeletal defects occur in *Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC)* β *syndrome*. The lobster-claw deformities of the hands and feet and cleft lip and palate enable the syndrome to be recognized easily.

Figure 1 Silver/pigment dilution of hair in a child with Griscelli syndrome

Table 1 Causes of pigmentary dilution of the skin, hair and eyes

Disorder	Genetic defect	Clinical features
Oculocutaneous albinism	Defects in melanin production due to mutations in the tyrosinase gene	Divided into four subtypes with a wide variation in color of hair and skin, ranging from a pigmentless condition (OCA-1A) to subtle pigmentary dilution (OA-1, OCA-1B, A2-4)
Hermansky-Pudlak syndrome (HPS)	Mutations in genes that encode components of the BLOC1/2/3	• Nine subtypes of HPS have been identified so far. • Associated with platelet dysfunction: repeated episodes of epistaxis, abnormal development of pulmonary fibrosis, inflammatory bowel disease and kidney disease
Cross syndrome		Diffuse pigmentary dilution, silvery hair, ocular anomalies and neurologic abnormalities (e.g., psychomotor retardation, ataxia and spasticity)
Chediak-Higashi syndrome (CHS)	Dysregulated fusion of primary lysosome like structures due to mutations in lysosomal trafficking regulator gene *LYST*, for a lysosomal transport protein	• Characteristic silvery sheen of the hair and skin with a skin color that is lighter than that of other family members • Photophobia, nystagmus and ocular hypopigmentation • Additional findings include a bleeding diathesis due to diminished function of platelet dense granules, progressive neurologic dysfunction and severe immunodeficiency due to abnormal lytic granules in lymphocytes, natural killer cells and neutrophils • Giant abnormal granules or melanosomes are the hallmark of CHS and result from dysregulated fusion of primary lysosome-like structures
Trichohepatoenteric syndrome (phenotypic diarrhea of infancy)	Autosomal recessive disorder caused by mutations in the tetratricopeptide repeat domain 37 gene (*TTC37*)	• Diffuse pigmentary dilution of the skin and hair, platelet defects (including abnormal granules) and immunodeficiency • Brittle hair with trichorrhexis nodosa, intractable diarrhea during infancy, primary liver disease, facial dysmorphism and cardiac defects
Griscelli syndrome (GS1, GS2 and GS3)	Due to mutation of proteins involved in melanosome transport and/or transfer *GS1:* Mutations in the gene that encodes myosin-Va *GS2:* Associated with mutation in *RAB27a* *GS3:* Associated with Leaden	• Pigmentary dilution of the skin and silvery-gray hair • *GSI:* Primarily neurologic impairment • *GSII:* Immune abnormalities, hemophagocytic syndrome can also occur with uncontrolled T-lymphocyte and macrophage activation leading to death • *Elejalde syndrome* presents with the pigmentary findings of GS plus severe neurologic dysfunction
Woolf syndrome/Ziprkowski-Margolis/albinism-deafness syndrome	X-linked disorder (gene locus Xq26.3-q27.1)	Congenital neural deafness and a severe piebaldism-like phenotype
Prader-Willi syndrome	Chromosomal and molecular changes of chromosome 15 at q11-q13 region	Light skin compared with relatives, normal to light hair, blue to brown irides, variable retinal pigment, normal to slightly reduced visual acuity. Neonatal hypotonic hyperphagia, obesity, developmental delay, mental retardation
Angelman syndrome	Same as Prader-Willi	• Besides hypopigmentation of hair, skin and eyes; growth retardation; developmental delay; mental retardation; ataxia; jerky gait; seizures • Dysmorphic facies (microcephaly, flat occiput, protuberant tongue)

Abbreviations: BLOC1/2/3, biogenesis of lysosome-related organelles complexes 1–3; OCA1 A, oculocutaneous albinism type 1A; OCA1 B-4, oculocutaneous albinism type 1B-4; GS1, Griscelli syndrome type 1; GS2, Griscelli syndrome type 2; GS3, Griscelli syndrome type 3.

The cutaneous features consist of diffuse hypopigmentation and dryness of the skin and hair.

Acquired nutritional deficiencies, especially with lack of copper and selenium can also cause hypopigmentation of the skin. It is seen in kwashiorkor but can also be seen in children receiving long-term parental nutrition. The hypomelanosis usually begins on the face. Hypomelanotic kwashiorkor responds to dietary protein, although the skin is said to repigment slowly.

The epidermis generally contains normal numbers of melanocytes and histology of the skin is not helpful in differentiating these conditions. The pathophysiological defect of hypopigmentation lies either in melanin biosynthesis or melanosome formation and trafficking. Disorder of melanin biosynthesis can be due to tyrosinase defects (occurring in OCA types 1 and 3 and copper deficiency) or melanosomal dysfunction (occurring in OCA types 2 to 4). Abnormalities in the formation, transport and transfer of melanosomes occur in Hermansky-Pudlak, Chediak-Higashi and Griscelli syndromes.

Localized Hypopigmentary Disorders

Localized hypopigmentation presenting in early childhood can be due to genetic or acquired causes. These disorders can clinically be categorized based on whether the lesions are depigmented or hypopigmented.

Vitiligo

Vitiligo is an acquired skin depigmentation disorder occurring in approximately 1% of the population worldwide. Although the exact etiopathogenesis is still not completely known and various theories have been proposed, but it is generally accepted to be an

autoimmune process directed against the melanocytes. It is not a life-threatening disease, but its association with a number of other autoimmune diseases as well as psychosocial difficulties causes significant impairment of quality of life in patients.

Clinically, vitiligo is classified into segmental vitiligo **(Fig. 2)** and nonsegmental vitiligo (NSV) **(Figs 3A and B)**, the latter including several variants (generalized vitiligo, acrofacial vitiligo, universal vitiligo). More recently, mixed vitiligo (MV) **(Figs 4A and B)** has been defined as the combination of initial segmental vitiligo followed by the occurrence of bilateral NSV patches several months, or more rarely, years later.

The presence of a family history for vitiligo, Koebner phenomenon, leukotrichia and associated autoimmune disorders such pernicious anemia, Addison disease, type 1 diabetes mellitus (T1DM), juvenile rheumatoid arthritis, alopecia areata and especially Hashimoto thyroiditis can support the diagnosis. On histological examination, a complete absence of melanocytes is reported except in early lesions where some persistent melanocytes can be found. Current common conventional treatment options include topical steroids, topical calcineurin inhibitors or UV therapy; all of them often with variable results **(Table 2)**.

Piebaldism

Piebaldism is a rare autosomal dominant disorder with an underlying defect of the tyrosine kinase transmembrane receptor on melanocytes (*KIT* gene), leading to an impaired embryonic migration and survival of melanocytes in the skin. Both piebaldism and vitiligo are characterized by an absence of epidermal melanocytes and the clinical presentation of depigmentation. However, unlike vitiligo, lesions in piebaldism are present at birth and remain stable throughout life. It is characterized by congenital, extensive, symmetrically distributed depigmented lesions mainly on forehead, front of the thorax and extremities. The extent of the lesions is variable, ranging from only a midfrontal poliosis or white

Figures 4A and B Segmental vitiligo transforming into generalized vitiligo (mixed vitiligo)

Figure 2 Segmental vitiligo over neck and upper back in a child

Figures 3A and B Nonsegmental or generalized vitiligo over extremities

Table 2 Treatment modalities for vitiligo

Treatment	Comments
Camouflage	Concealers and cosmetics
Topical steroids	Potent or moderately potent steroids like clobetasol propionate, betamethasone, fluocinonide or mometasone
Calcineurin inhibitors	Tacrolimus/pimecrolimus
Vitamin D analogues	Calcipotriol, calcitriol
Phototherapy and laser	NBUVB/PUVA (systemic or topical) and excimer laser
Systemic	Oral steroids, dexamethasone (oral mini pulse)
Depigmentation	Monobenzone 20% cream
Surgical grafting	Suction blister, split thickness grafts, punch grafting, melanocytes suspension and culture

Abbreviations: NBUVB, narrow band ultraviolet B radiation; PUVA, psoralen ultraviolet A radiation.

Table 3 Clinical types of Waardenburg syndrome

WS type I	*PAX3*, a gene critical for both melanocyte migration and facial embryogenesis	White forelock, heterochromia irides, cutaneous depigmentation and congenital sensorineural deafness with a characteristic facies
WS type II	• *MITF* gene • *SNAI2* or *SOX10* transcription factors: migration and development of neural crest cells	No facial characteristics but iris pigmentary changes and deafness are common
WS type III	*PAX3*	Musculoskeletal abnormalities and rarely associated neural tube defects
WS type IV	• Endothelin 3 • Endothelin B receptor • *SOX10*	Normal face pigmentary defects and sensorineural deafness in association with absence of enteric ganglia in the distal part of the intestine (Hirschsprung disease)

Abbreviations: WS, Waardenburg syndrome; *MITF*, microphthalmia-associated transcription factor.

forelock **(Fig. 5)** (present in 80–90% of the patients) and minimal areas of depigmentation to a depigmentation of almost the entire body and hair. Another differentiating feature is presence of hyperpigmented macules within the areas of depigmentation. Management includes photoprotection and camouflage. Surgical grafting techniques like split thickness or blister grafting and non-cultured melanocyte suspension are a good therapeutic option for stable depigmentation as in piebaldism. In patients presenting with signs of piebaldism, it is important to check for features of Waardenburg syndrome (WS).

Waardenburg Syndrome

This is a group of autosomal dominant disorders characterized by a white forelock, heterochromia irides, cutaneous depigmentation, and in many patients, congenital sensorineural deafness. It is of four types **(Table 3)**. Individuals with Waardenburg syndrome (WS) type 1, the most common form, have characteristic facial features, including a broad nasal root and lateral displacement of the medial canthi and lacrimal puncta of the lower eyelids (dystopia canthorum). In WS type 2, the microphthalmia-associated transcription factor (*MITF*) gene is mutated and mutation of the same gene can also lead to Tietze syndrome. Tietze syndrome is clinically distinguishable

from WS type 2 in that the former is characterized by a more severe phenotype presenting with generalized instead of patchy hypopigmentation; and complete instead of variable hearing loss.

Single Hypopigmented Macule

In an infant who presents with a single hypopigmented macule or patch, the main differential diagnoses are nevus depigmentosus (ND), an ash leaf macule of tuberous sclerosis, and nevus anemicus.

Nevus depigmentosus It is a common localized hypomelanosis seen in children which becomes apparent at birth or in the 1st year of life and although it increases in size and does not change in shape **(Figs 6A and B)**. It may be confused with segmental or focal vitiligo during the first few years. Skin inspection with Wood's lamp examination helps in diagnosis as the ND is characterized by hypopigmentation rather than a depigmentation, as seen in vitiligo. There are three subtypes of the ND: (i) an isolated form (solitary and well-defined lesions), (ii) a segmental form (unilateral, band-haped lesions, sometimes Blaschkoid distribution) and (iii) systematized form [extensive whorls and streaks of hypopigmentation, following the lines of Blaschko (hypomelanosis of Ito or pigmentary mosaicism)].

Nevus anemicus It is a localized vascular anomaly in which the vessels are hypersensitive to catecholamines **(Fig. 7)**. Using diascopy, nevus anemicus can be made to blend into the surrounding blanched skin. Nevus anemicus is not accentuated by Wood's lamp, in contrast to lesions which contain less melanin. The reflex vasodilatory response is also absent upon application of pressure and heat; scratching a line across nevus anemicus will not induce erythema in the lesion and the contrast can be seen in the surrounding normal skin.

The diagnosis of *tuberous sclerosis* (TS) becomes more likely if there are multiple hypomelanotic macules **(Fig. 8)** or if the lesion is lance-ovate shape like ash leaves (rounded at one end and pointed at the other). Ash leaf macules are usually the first manifestation of TS and the other cutaneous features, such as facial angiofibromas, start appearing after the age of 5 years.

Figure 5 White forelock in piebaldism

Figures 6A and B Nevus depigmentosus over forehead and arm

Figure 7 Nevus anemicus on the face

Figure 8 Multiple hypopigmented macules in tuberous sclerosis

Pigmentary Mosaicism

The lines of Blaschko are believed to be pathways of migration and proliferation of epidermal cells during embryogenesis. The bands of abnormally pigmented skin are clones of cells carrying a mutation in a gene expressed in the skin. Clinically, these disorders present with linear pigmentary changes as one of their features. The linear or segmental variant of ND, hypomelanosis of Ito, and linear and whorled hyperpigmentation are a phenotypic spectrum of such genetic mosaicism and have recently been classified under the term *pigmentary mosaicism*.

Hypomelanosis of Ito is a descriptive term for streaks of hypopigmentation that presents in infancy. It is not a specific diagnosis and it may occur as a result of different chromosomal abnormalities that disturb various genes involved in skin pigmentation. Although the characteristic configurations are whorled and linear, the lesions can be patchy as well **(Fig. 9)**. On the other hand, there is a variant of ND that consists of segmental or linear hypopigmentation and this overlaps with hypomelanosis of Ito clinically. Some clinicians have used the term *nevoid linear hypopigmentation* to encompass both conditions. It is pertinent to evaluate for associated systemic abnormalities affecting the central nervous, musculoskeletal systems and the heart, which occurs in about one-third of children, when the diagnosis of hypomelanosis of Ito is considered.

Figure 9 Blaschkoid hypopigmented lesions in hypomelanosis of Ito

The common differentials to be considered for linear hypopigmentation are: lichen striatus **(Fig. 10)**, linear scleroderma, linear lichen sclerosis, postinflammatory or traumatic changes, incontinentia pigmenti stage IV **(Fig. 11)** and Goltz syndrome.

Figure 10 Lichen striatus hypopigmented papules on the arm

Figure 11 Hypopigmented and hyperpigmented macules in stage IV of incontinentia pigmenti

ONSET IN LATER CHILDHOOD

Most of these are acquired in origin. Similar to those presenting in early childhood, these diseases can be clinically divided into those characterized by generalized hypopigmentation and those causing localized disease **(Box 1)**.

Generalized Hypopigmentation

Generalized hypopigmentation presenting in an older child is uncommon. The causes include vitiligo universalis, inborn errors of metabolism (phenylketonuria, homocystinuria and histidinemia), malnutrition (in particular copper and selenium deficiency) and a delay in the diagnosis of an infancy-onset pigmentary dilutional disorder. The inborn errors of metabolism are discussed in detail in Section 3 on metabolic disorders.

Localized Hypopigmentary Disorders

Hypopigmentary disorders presenting in later childhood are usually localized. The common causes of acquired hypopigmentation are infections, autoimmune or lymphoproliferative **(Box 1)**.

BOX 1 Acquired hypopigmentary disorders

- *Generalized hypopigmentary disorders*
  Vitiligo universalis, inborn errors of metabolism (homocystinuria and histidinemia), malnutrition (in particular copper and selenium deficiency)
- *Localized hypopigmentary disorders*
  Vitiligo; pityriasis alba; pityriasis versicolor; postinflammatory hypopigmentation: pityriasis lichenoides chronica and lichen striatus; infections: leprosy; atrophy: lichen sclerosus, morphea and the hypopigmented variant of mycosis fungoides.

Pityriasis Alba

Pityriasis alba (PA) is a common, benign condition which may be confused with Hansen disease, pityriasis versicolor and hypopigmented mycosis fungoides (HMF), especially when it occurs on extra facial sites. It typically presents as ill-defined hypopigmented patches with minimal fine scale on the face or trunk **(Fig. 12)**. PA is associated with atopic dermatitis. Treatment involves emollients and low to moderate potency corticosteroid creams as well as photoprotection.

Postinflammatory Hypopigmentation

This is a common cause of acquired hypopigmentary disorders. It can occur following cutaneous inflammation, injury or dermatological treatment. Most cases of postinflammatory hypopigmentation improve spontaneously within weeks or months if the primary cause is treated or taken care of; however, it can be permanent if there is complete destruction of melanocytes. It is commonly seen following atopic dermatitis as well as other forms of eczema **(Fig. 13)**. The decrease in pigmentation can be the result of a disruption in the transfer of melanin to keratinocytes secondary to the inflammatory process or the application of potent topical corticosteroids. In addition, postinflammatory hypopigmentation in children can also be due to pityriasis lichenoides chronica **(Fig. 14)** and lichen striatus. When an older child presents with

Figure 12 Pityriasis alba, hypopigmented scaly patches on face

Figure 13 Postinflammatory hypopigmentation after resolution of atopic eczema

Figure 14 Postinflammatory hypopigmentation after pityriasis lichenoides chronica

Figure 15 Postinflammatory depigmentation in infantile lupus erythematosus

widespread 3–6 mm macular hypopigmentation, pityriasis lichenoides chronica should be considered. In lichen striatus, the hypopigmentation is typically linear following the lines of Blaschko and multiple small, flat-topped papules may be seen. Postinfectious hypopigmentation can result from superficial cutaneous infections as well as childhood viral exanthems and varicella. Post-traumatic hypopigmentation is also not uncommon in children due to the frequent superficial injuries they sustain.

Collagen Vascular Disorders

Hypopigmentation is also rarely seen in lesions of localized scleroderma (morphea) and systemic sclerosis and lupus erythematosus **(Fig. 15)**. The lesions may mimic vitiligo and the clues to the diagnosis of scleroderma include the presence of perifollicular hyperpigmentation (forming a *salt* and *pepper* dyschromatosis) and induration of the dermis. The epidermal melanocytes in the interfollicular regions disappear, but those in the near vicinity of hair follicles are retained. This is in contrast to vitiligo in which melanocytes in both regions are affected. In repigmenting vitiligo, repigmentation typically starts in the perifollicular region, and differentiating it from scleroderma can sometimes be difficult.

MANAGEMENT OF HYPOPIGMENTED DISORDERS

Treatment for many hypopigmented disorders is limited, especially those which are congenital in origin. Hypopigmented diseases with an associated inflammatory component like vitiligo, lichen striatus, lichen sclerosis and postinflammatory hypopigmentation may be treated with topical corticosteroids and calcineurin inhibitors when lesions are limited and with phototherapy when lesions are widespread and the child is older. Autologous grafting of cultured and noncultured melanocytes has been used successfully to treat stable vitiligo and piebaldism.

The importance of sun protection, including the use of a broad-spectrum sunscreen on hypopigmented lesions, should be emphasized to patients and parents. Hypopigmented lesions are more susceptible to sun damage and the lesions will be more obvious with the differential tanning response compared with the surrounding normal skin. In addition, Koebner phenomenon may lead to spreading of vitiligo.

Cosmetic cover-ups for camouflage may be the only option in some hypopigmented disorders. Topical tanning products containing dihydroxyacetone may be used on the lesions to decrease the color disparity with the normal skin.

The psychosocial aspect of the patient is an important integral part of management, especially in school children when the hypopigmentary disorder can be the source of significant embarrassment and psychological trauma to the developing child. Cooperation and regular communication between the physician, parents and school is essential, and enrolling the help of counselors and child psychiatrists should be instituted early when appropriate.

MORE ON THIS TOPIC

Lio PA. Little white spots: an approach to hypopigmented macules. Arch Dis Child Educ Pract Ed. 2008;93:98-102.

Mollet I, Ongenae K, Naeyaert JM. Origin, clinical presentation, and diagnosis of hypomelanotic skin disorders. Dermatol Clin. 2007;25:363-71.

Patel AB, Kubba R, Kubba A. Clinicopathological correlation of acquired hypopigmentary disorders. Indian J Dermatol Venereol Leprol. 2013;79:376-82.

Ruggieri M, Pavone L. Hypomelanosis of Ito: clinical syndrome or just phenotype? J Child Neurol. 2000;15:635-44.

Sori T, Nath AK, Thappa DM, Jaisankar TJ. Hypopigmentary disorders in children in South India. Indian J Dermatol. 2011;56:546-9.

Tey HL. A Practical classification of childhood hypopigmentation disorders. Acta Derm Venereol. 2010;90:6-11.

Treat J. Patterned pigmentation in children. Pediatr Clin North Am. 2010;57:1121-9.

van Geel N, Speeckaert M, Chevolet I, et al. Hypomelanoses in Children. J Cutan Aesthet Surg. 2013;6:65-72.

Chapter 48.6
Atopic Dermatitis
Deepak A Parikh, Abhijit Saha

Atopic dermatitis (AD) is an itchy, chronic or chronically relapsing inflammatory skin disorder predominantly affecting children and young adult. It is characterized by papulovesicular eruption which gets lichenified with typical flexural distribution. Pathogenesis is complicated. In nutshell, it is a complex interplay of four factors: (i) genetic, (ii) environmental, (iii) immunological and (iv) defective skin barrier responsible for phenotypic expression of the disease.

CLINICAL FEATURES

Clinical features of AD can be described in three different phases: (i) infantile phase up to 2 years of age, (ii) childhood phase from 2 years to puberty and (iii) adult phase from puberty onward. Each of the phases has typical distribution and morphological pattern, though considerable overlap may occur. Morphologically, lesions may be acute weeping eczema mainly seen in infantile AD, subacute with erythematous scaly plaque and chronic AD with lichenified plaque. Infantile eczema typically starts from face, scalp and gradually involves external aspects of extremities and trunk with sparing of the diaper area. In childhood, lesions predominantly involve flexural areas, antecubital and popliteal fossae being most common. Lichenification first appears in this phase. Adult AD has predilection for face, hand, wrist, dorsal feet and back. Involvement of certain specific sites is worth mentioning during childhood; lip (cheilitis), retroauricular area (fissuring) and periorificial area. A number of associated physical findings are frequently seen in AD. Few important ones are ichthyosis, xerosis, keratosis pilaris, hyperlinearity of palm and sole, dennie-morgan fold (infraorbital fold), pityriasis alba and thinning or absence of lateral eyebrows (Hertoghe's sign). Potential complications are *Staphylococcus aureus* colonization, Kaposi varicelliform eruption due to herpes simplex virus infection and exfoliative dermatitis.

TREATMENT

Most important aspect of treatment is education of the parents with proper explanation of natural course of the disease; avoidance of allergen, harsh detergent and irritants such as synthetic and woolen cloths; prompt treatment of intercurrent infection and adherence to prescribed treatment. Physician should be flexible enough and treatment should be individually tailored. Bathing should be done with lukewarm water with oil emollient and syndet bar favoring skin pH. Contact with water should be restricted to 10–15 min and skin should be patted dry avoiding rubbing and followed immediately with liberal use of ceramide containing emollient when the skin is still slightly humid.

Traditional reactive approach with topical steroid is to application to the lesional skin only and gradually tapered off with clearance of the lesion. This approach has been challenged by predefined, long-term, low dose topical steroid applied to the previously affected sites with liberal use of emollient for entire body. This proactive approach significantly reduces risk of relapse. Potency of steroid should be determined on the basis of age of the patient, site, extent and severity of involvement. For children, mild to moderately potent steroid is favored; as also in face, eyelids, genitalia and intertriginous areas.

Topical calcineurin inhibitors (TCIs) (tacrolimus 0.03% ointment and pimecrolimus 1% cream) have emerged as second-line therapy for short-term, noncontinuous use in children of more than 2 years of age who do not respond adequately to topical steroid or where steroid is contraindicated. In contrast to topical steroids, TCIs do not cause skin atrophy or telangiectasia, so can be safely used in eyelid, perioral and intertriginous areas. Most frequent side effects are transient burning and warmth sensation which decrease with continuous use. Proactive therapy with TCIs reduces severity and number of flares. Increased risk of malignancy and eczema herpeticum is still to be established.

Other modalities are topical and systemic antibiotics only when active skin infection is present, sedating antihistaminic, phototherapy and systemic agents such as systemic steroid, methotrexate, cyclosporine and many more.

DIFFERENTIAL DIAGNOSIS

Seborrheic Dermatitis

Infantile seborrheic dermatitis (ISD), a common disorder of infancy usually starts in the 1st month of life and resolves within 4–6 months. This is characterized by yellowish, greasy, thick, adherent scales on vertex and frontal area of the scalp; whereas lesions over face, eyebrows, nasolabial folds and retroauricular region are round to oval areas of inflammation with fine, branny scales. Rashes over intertriginous areas are less scaly but macerated and eroded. Lack of pruritus may be due to immature scratch reflex. Infants with ISD do not have increased tendency to develop seborrheic dermatitis in adulthood but may develop AD or psoriasis in near future. Napkin dermatitis may be a presenting feature. It is very difficult to differentiate this entity from atopic dermatitis. Age of onset after 2nd month, pruritus and involvement of signature sites in addition to cheek and forehead may favor atopy to some extent. Treatment options are use of mineral oil to soften the crust, topical steroid with antifungal, ketoconazole shampoo, etc.

Juvenile Plantar Dermatosis

This entity is characterized by symmetrical, shiny erythema with occasional peeling and fissuring of the forefoot and great toe with occasional pruritus and sparing of interdigital spaces. Juvenile plantar dermatosis (JPD) is frequently associated with personal or family history of atopy. Uses of occlusive shoes or synthetic shocks and friction have been implicated as precipitating events in school going children. Emollient, topical steroids, topical tacrolimus and use of cotton shocks and sandals are beneficial.

Papular Urticaria

Papular urticaria commonly occurs on the lower leg, face, scalp in sensitized children. Classical lesion is punctum surrounded by wheal. Lesions are often excoriated. Primary lesion may be bullae. Patients often respond to topical steroids and antihistaminics.

Prurigo Nodularis

Lesions of prurigo nodularis are discrete, extremely pruritic, excoriated, hyperkeratotic, pigmented nodules with occasional crusting and scaling distributed mainly over extensor aspects of lower extremities. Etiology is unknown. Common secondary causes are insect bite, folliculitis, atopic dermatitis, Hodgkin lymphoma, leukemia and liver disease. Treatment modalities such as emollient, topical steroid with or without occlusion, topical calcipotriol, intralesional steroid and sedating antihistaminic are effective. Recalcitrant cases respond to narrow-band ultraviolet B (UVB) and other systemic modalities such as cyclosporine. Treatment of underlying cause should be considered as and when required.

Nummular Dermatitis

Nummular dermatitis is characterized by well defined, coin shaped, extremely pruritic, excoriated patches formed by confluence of papules and vesicles with oozing and crusting distributed over extensor aspects of extremities and trunk. Disseminated nummular dermatitis may be a presentation of atopic dermatitis. Other etiological factors may be hypersensitivity to bacterial antigen, contact allergen, emotional stress and nutritional deficiency. Patients can be managed with wet compression for oozing lesions, emollient, topical steroid and immunomodulators, topical or systemic antibiotic as indicated and antihistaminic. Prognosis is chronic and relapsing.

Lichen Striatus

Lichen striatus usually occurs in the age group between 9 months and 9 years. Asymptomatic, skin colored to erythematous lichenoid papules coalesce to form linear plaque over lower extremities and trunk along the Blaschko line. Nail dystrophy may be a potential complication. Disease is self-limited.

Perioral Dermatitis

Perioral dermatitis, more specifically periorificial granulomatous dermatitis, is a disorder of unknown etiology characterized by discrete, small, firm, dome-shaped, flesh-colored papules without perceptible erythema involving the perioral, periorbital and perinasal areas. Prognosis is good. Different treatment modalities are topical metronidazole, TCIs and oral antibiotics (doxycycline > 9 years of age, erythromycin < 9 years of age).

MORE ON THIS TOPIC

Dhar S, Banerjee R. Atopic dermatitis in infants and children in India. Indian J Dermatol Venereol Leprol. 2010;76:504-13.

Inamadar AC. Lichen striatus with nail involvement. Indian J Dermatol Venereol Leprol. 2001;67:197.

Kanwar AJ, De D. Epidemiology and clinical features of atopic dermatitis in India. Indian J Dermatol. 2011;56:471-5.

Lipozencic J, Ljubojevic S. Perioral dermatitis. Clinics Dermatol. 2011;29:157-61.

Moises-Alfaro CB, Caceres-Rios HW, Rueda M, et al. Are infantile seborrheic and atopic dermatitis clinical variants of the same disease? Int J Dermatol. 2002;41:349-51.

Thaci D, Reitamo S, Gonzalez Ensenat MA, et al. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. Br J Dermatol. 2008;159:1348-56.

Thaci D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. Clin Dermatol. 2010;28:52-6.

Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis--an emerging concept. Allergy. 2009;64:276-8.

Chapter 48.7
Contact Dermatitis
Raghubir Banerjee, Sandipan Dhar

The condition in which skin is inflamed due to the exposure to a chemical irritant or a sensitizer is grouped as contact dermatitis. This is a spectrum which encompasses irritant contact dermatitis (ICD) at one end and allergic contact dermatitis (ACD) at the other. There may be some overlap in the clinical presentation as acute form overlaps to subacute or the chronic variety, but they are quite different etiologically. The other common forms include photocontact dermatitis and contact urticaria. Contact dermatitis is being diagnosed more frequently in teenagers due to increasing use of cosmetics and perfumes.

EPIDEMIOLOGY

The incidence of contact dermatitis in children is on the rise. Contact dermatitis may be the presenting dermatosis in some children. The irritant variety is not commonly observed except in industrial areas where the child's hands bear more of the insult mostly from the use of cleansing agents and soaps. Diaper dermatitis can also occur because of an irritant that may be present in the child's excreta or the diaper itself.

There is no racial predisposition but girls outnumber boys when it comes to the incidence of allergic contact dermatitis. Topical mercurochrome, neomycin and nickel are the common offending irritants.

PATHOPHYSIOLOGY

Irritant contact dermatitis results due to an inflammation from skin damage or irritation caused by contact with certain chemical substances. The skin damage results in the liberation of mediators of inflammation from the keratinocytes which initiate the process.

The phenomenon of delayed hypersensitivity reaction is sufficient to explain the chain of events leading to ACD. The offending substances usually are of lower molecular weight. These haptens are capable of binding to carrier proteins to initiate the reaction with their location on the langerhans cell. The primary sensitization process occurs with the help of the lymphatic system and may take about 2 weeks or so to develop after exposure to the specific allergen. After the initiation, ACD develops promptly on re-exposure to the contact allergen. In some instances, a weak sensitizer may initiate the process following long-term exposure. This is typically seen in some chronic cases of hand eczema.

Contact dermatitis may also be exacerbated by sun exposure. The role of a phototransformed allergen comes into play causing either an irritant or an allergic reaction. In rare instances, a wheal reaction may occur which is labeled as contact urticaria.

CLINICAL FEATURES

Irritant contact dermatitis often presents with well-demarcated area of dermatosis with erythema, vesiculation, thickening of skin or fissuring. The tendency to spread is less compared to the allergic variety and can be doubly confirmed by a negative patch test result to the allergens. Constant friction due to itching causes the usual changes of eczematization.

Individuals may develop a habit of rubbing the site affected by ICD and may develop secondary lichenification. The lesion of longstanding ACD may spread from localized areas like the hands and feet to involve larger body surfaces and may manifest as erythroderma in some cases. Some topical applications can often irritate the perianal region in infants. Facial involvement like the eyelids can raise suspicion of the role of airborne allergens.

DIAGNOSIS

The contact of the affected area to the specific chemical irritant is the clue to the diagnosis of ICD which can be further confirmed by a negative patch test result in such cases. In acute cases, a quick onset and a stinging sensation far in excess of pruritus should help the clinician to suspect the condition. In some instances, a delayed onset may be noted and this is typical of delayed onset or cumulative ICD. Children who are atopic or suffering from atopic dermatitis are more prone to develop primary ICD. Hands are commonly involved in such cases. The chemicals to which the child is commonly exposed should be subjected to diagnostic patch testing for proper evaluation.

The battery of patch test chemicals forms the cornerstone of the investigative machinery. The reported lowest age of patch tested child is about 2 years. Almost half the cases of this condition can be confirmed by a positive patch test reaction. The standard procedure or method uses Finn's chambers to keep the chemicals under occlusion and the result is noted on removal after 48–72 hours of application.

A positive patch reaction may show just a sensitivity reaction and not necessarily the cause of contact dermatitis in affected children. Some common allergens seen in patch test are nickel, rubber chemicals, paraphenylenediamine, fragrances and preservatives in cosmetics.

The role of a skin biopsy and histopathological examination are limited to confirming its eczematous (spongiotic) nature and ruling out other diseases.

TREATMENT
Irritant Contact Dermatitis
Moisturizers like petrolatum are cheap and effective to act as barrier repair agents though lipid rich creams and ceramides are also quite useful in these cases. Neutral cleansers and syndets are useful adjuncts as they do not alter skin pH. Topical corticosteroids and immunomodulators have variable response in treating such patients.

The role of prevention is more important in those cases. The use of moisturizers and emollients helps to reduce the chemical-induced skin damage as does the barrier cream formulations. The preventive role of dimethicone and aluminum chloral hydrate in barrier creams is well documented. Moisturizers with high lipid content and those with urea, ceramides, lactic acid and also fabric softeners play a similar role.

Allergic Contact Dermatitis
Oral antihistamines help to reduce the associated pruritus. Saline or oatmeal compresses have a soothing effect for oozing vesicular lesions. Acute conditions are usually managed with short course oral steroids, but mostly topical corticosteroids are used as the mainstay of treatment. In children, mometasone and fluticasone

are the commonly used molecules. They show improved efficacy when used in conjunction with emollients and barrier creams. Topical calcineurin inhibitors like tacrolimus and pimecrolimus are the alternate line of drugs which act as immunomodulators and are used in children. In some chronic recalcitrant cases, oral cyclosporine, azathioprine and biologicals have also shown beneficial effects.

PROGNOSIS

The number of sensitizers in the environment is unending and hence a careful history to pinpoint the offending agent is crucial for diagnosis and further management to prevent and treat this condition.

MORE ON THIS TOPIC

Fisher AA, Rietschel RL, Fowler JF. Fisher's Contact Dermatitis. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 1995.

Mallory S, Bree AF, Chern P. Illustrated Manual of Pediatric Dermatology: Diagnosis and Management. UK: Taylor & Francis; 2005.

Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence. 4th ed. Philadelphia: Elsevier Saunders; 2011.

Chapter 48.8
Urticaria and Mastocytosis
Deepika Pandhi, Rahul Arora

URTICARIA

Urticaria, commonly known as hives, affects 15–25% of people at some point in their lifetime. In most cases, the disorder is relatively mild, although recurrent and frustrating for both the patient and the physician. It is also a common problem amongst the pediatric population, although population-based studies evaluating its prevalence are scarce.

ETIOLOGY

Urticaria is defined by the presence of wheals and/or angioedema **(Fig. 1)**. It is broadly classified into acute and chronic urticaria depending upon duration of onset **(Fig. 2)**. Acute urticaria lasts for less than 6 weeks and is more common than chronic urticaria that lasts longer. **Table 1** depicts the common etiological associations of acute and chronic urticaria in childhood. Common causes are discussed below.

Acute Urticaria

A cause can be identified in 20–90% cases.

Infections

Infections have been found as the most common cause of trigger of pediatric acute urticaria. Usual infections include upper respiratory tract infections, gastrointestinal and genitourinary infections. Viruses, such as adenovirus, enterovirus, rotavirus, respiratory syncytial virus, Epstein-Barr virus and cytomegalovirus, and bacteria, such as *Streptococcus* as well as *Mycoplasma pneumoniae,* may induce urticaria in children. Parasitic infections, including *Blastocystis hominis*, *Plasmodium falciparum* and *Anisakis simplex,* have also been reported to trigger urticaria. The exact role of infections in pathogenesis of mast cell triggering remains elusive.

Drugs

Drug hypersensitivity is the second main suspected cause in childhood acute urticaria. The most commonly reported drugs are antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).

Food Allergy

Immunoglobulin E (IgE)-mediated food allergy may present as urticaria. It may occur after direct skin contact, inhalation or
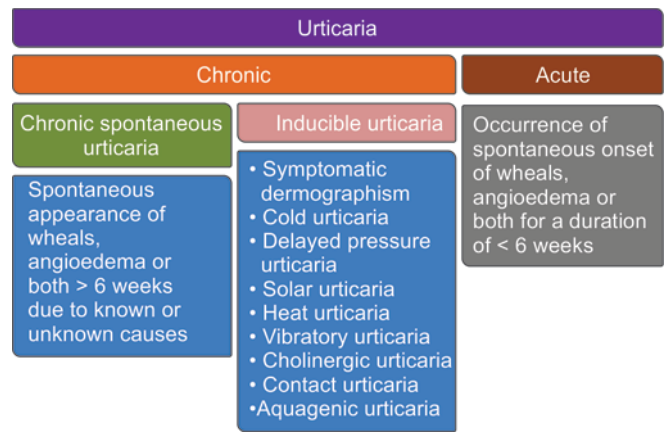
Figure 2 Classification of urticaria

Table 1 Etiological associations of urticaria

Acute urticaria	Chronic urticaria
Drugs	Idiopathic
Infections	Autoimmune
Atopy	Physical
Food allergy	Food additives
Aeroallergens	Drugs
Idiopathic	Aeroallergen
	Parasites
	Infections
	Thyroid diseases
	Collagen vascular disease

ingestion. The symptoms occur immediately in less than 1 hour after food ingestion. Oral food challenges are the gold standard for diagnosis.

Chronic Urticaria

Infections

Several pathogens have been associated with pediatric chronic urticaria, including viruses (e.g., Epstein-Barr virus), bacteria (mostly streptococci, staphylococci, *Helicobacter pylori* and *Escherichia coli*) and parasites.

Autommunity

Autoreactivity can be assessed in vivo by the autologous serum skin test (ASST). Positive ASST indicates the presence in the
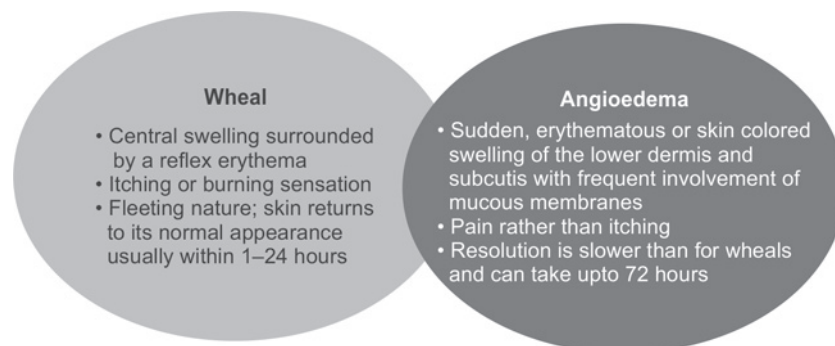
Figure 1 Wheals and angioedema
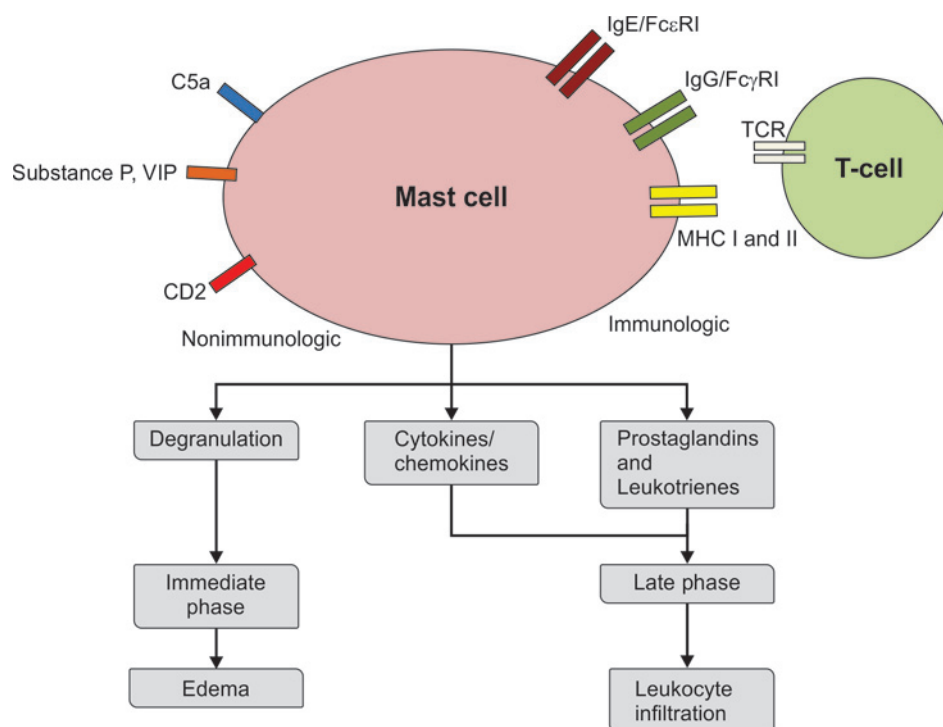
Figure 3 Pathophysiology of urticaria and mast cell degranulation

Abbreviations: VIP, vasoactive intestinal peptide; MHC, major histocompatibility complex; TCR, T-cell receptor; IgE, immunoglobulin E; IgG, immunoglobulin G; CD2, cluster of differentiation 2

patient's serum of factors (which may include autoantibodies) that are responsible for the development of wheals. Frequency of positive ASST in childhood chronic spontaneous urticaria ranges between 38% and 47%.

Physical Urticaria

Physical urticaria may present as varied manifestations alone or in combination. This occurs mostly secondary to heat, pressure, cold or water.

PATHOPHYSIOLOGY

Histamine is the most important mediator of urticaria. A variety of immunologic, nonimmunologic, physical and chemical stimuli may be responsible for the degranulation of mast cell granules and the release of histamine into the surrounding tissue and circulation. **Figure 3** delineates the mechanism of mast cell degranulation leading to urticaria.

Autoimmunity and Urticaria

Immune tolerance is maintained by a balance between autoreactive lymphocytes and regulatory mechanisms that counteract them. An increase in number and/or function of naturally occurring autoreactive T-cells, i.e., regulatory T-cells (Tregs) or diminished regulator mechanism manifests as autoimmunity. The autoimmune origin of chronic urticaria is further validated by findings suggested in **Box 1**.

Nonimmune-Mediated Urticaria

Complement-mediated urticaria includes urticaria that occurs following viral and bacterial infections, serum sickness and transfusion reactions. Certain drugs (opioids, vecuronium, succinylcholine, vancomycin and others) as well as radiocontrast agents cause urticaria due to direct mast cell degranulation through

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BOX 1 Autoimmune origin of urticaria

Indicators of autoimmunity in urticaria
- High prevalence of antithyroid antibodies
- Intradermal injection of autologous serum leading to wheal-flare response
- Presence of IgG antibody directed to the alpha subunit of the IgE receptor
- Positive association with HLA subtypes (DR4) and DQB (DQ8).
- Therapeutic response to plasmapheresis and IVIG.

Abbreviations: HLA, human leukocyte antigen; IVIG, intravenous immuno-globulin; IgG, immunoglobulin G; IgE, immunoglobulin E.

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a non-IgE-mediated mechanism. Urticaria from NSAIDs may be IgE-mediated or due to mast cell degranulation. Physical urticaria, in which some physical stimulus causes urticaria, includes immediate pressure urticaria, delayed pressure urticaria, cold urticaria and cholinergic urticaria. Despite exhaustive evaluation and workup, sometimes no cause can be found and this entity is known as *idiopathic urticaria*. Although, many of these cases are chronic autoimmune urticaria as defined by a positive ASST.

CLINICAL FEATURES

The primary manifestations of urticaria are pruritic wheals **(Fig. 4)** which usually the patient tends to rub and permanent hyperpigmentation or hypopigmentation is rare. In severe disease, systemic symptoms like wheezing, dyspnea, dizziness, headache and flushing may manifest. There may be spontaneous periods of remission and disease may manifest episodically.

A patient of chronic urticaria may present with both wheals and angioedema at the same time. The lesion severity is more in the evening. There may be variation in severity over time. In dermographism, the lesions are polymorphic and assume the shape of provoking stimulus applied **(Fig. 5)**.

Figure 4 Multiple erythematous wheals of acute urticaria in a child

Figure 5 Linear wheals (dermographism) over the trunk

Angioedema presents as a usually transient, localized, nonpitting, nonpruritic swelling of the deep dermis mostly affecting the face, extremities and genitalia. Swellings involving the tongue, pharynx or larynx may present with life-threatening dyspnea due to laryngeal edema.

An approach to history and examination to a child with urticaria is delineated in **Box 2**. Further tests may be done in patients with history suggestive of physical urticaria to elicit a demonstrable response **(Table 2)**.

DIFFERENTIAL DIAGNOSES

Amongst a list of differentials **(Box 3)** that may be considered, urticarial vasculitis is the most important. It may be considered in patients with lesions lasting longer than 24 hours or when lesions are associated with more pain than itching and/or when lesions resolve with pigmentary changes or scaling.

MANAGEMENT

Box 4 details the list of work-up recommended for patient of urticaria. A detailed and extensive work-up is usually not

recommended in cases of acute urticaria as the diagnosis is usually clinical. In cases presenting with angioedema without urticaria, C4 levels should be documented and other investigations include C1q and C1 levels.

Table 2 Physical urticaria and its elicitation

Physical urticaria	
Dermographism	Itchy wheals occur in minutes, lasting less than 1 hour after: • Firm stroking of the skin with a smooth blunt object (back preferable) • A calibrated dermographometer set at 36 g/mm or less
Delayed pressure urticaria	Sustained pressure is applied to the back, shoulder or thigh: • 4.5 kg weighted rods with a 1.5 cm diameter applied for 15 min • Dermographometer set at 100 g/mm^2 pressed against the back of the shoulder for 70s, read after 2–6 hours and next day • Hanging a weight 15 lbs (7 kg) by a broad strap from a shoulder results in a wheal, often painful, at the application site 4–6 hours later, lasting from several hours up to 24 hours
Cholinergic urticaria	Raising the core body temperature by 0.7–1.0°C by: • Exercise in a hot environment until sweating • Hot bath (42°C) for 15 min induces itching with widespread small wheals within minutes
Cold urticaria	Application of a melting ice cube in a thin plastic bag for up to 20 min results in an itching wheal at the site within minutes of removal
Solar urticaria	Exposure to sunlight or solar simulator induces redness, itchy wheals at site of exposure within a few minutes lasting less than 1 hour
Aquagenic urticaria	Exposure of skin to water at body temperature in a bath for 15 min induces small itchy wheals on the immersed site within minutes
Heat contact urticaria	Whealing occurs in minutes localized to the site of application of heated objects at 39–45°C for 2–5 min lasting less than 1 hour
Vibratory angioedema	Application of a laboratory vortex resting on the forearm or finger for 1–5 min results, within minutes, in a red swelling of the vibrated area, lasting less than 1 hour

BOX 2 Approach to history and examination of patients with urticaria

History

- Time of onset
- Frequency/duration
- Diurnal variation
- Associated angioedema
- Associated pain, itch
- Family history
- Previous allergies
- Psychiatric diseases

- Surgical implantations
- Gastric/intestinal problems
- Induction by physical agents or exercise
- Drug history
- Correlation with food
- Correlation with menses

- Smoking
- Work profile
- Hobbies
- Stress
- Quality of life impact
- Response to therapy
- Previous diagnostic tests

Examination

- Polymorphic lesion that vary from several millimeters to large, continuous edematous plaques that have smooth surfaces with polycyclic curved borders
- The lesions are nonscaly but show an intense erythema and a trailing clearing region in older areas which may lead to a target configuration in expanding plaques
- The advancing border shows a discrete edge followed by a faint, trailing, diffuse border.

Simple tests to elicit physical urticaria (detailed in Table 2)

BOX 3 Differential diagnoses of urticaria

- Acute febrile neutrophilic dermatosis
- Atopic dermatitis
- Bedbug bites
- Contact dermatitis, allergic
- Erythema multiforme
- Fixed drug eruptions
- Insect bites
- Mastocytosis
- Reticular erythematous mucinosis
- Scabies
- Schnitzler syndrome
- Urticarial vasculitis
- Wells syndrome (Eosinophilic cellulitis)

BOX 4 Diagnostic work-up of urticaria

Investigations
- Generally no investigations for acute urticaria
- Complete blood count
- Absolute eosinophil cell count
- Stool for ova and parasites
- ESR, ANA, CRP, rheumatoid factor
- Hep B and C antibodies
- Serum cryoglobulins
- C3, C4 and C1 esterase inhibitor functional assays
- Thyroid function tests and antithyroid peroxidase (TPO) antibodies.

Abbreviations: Hep B and C, hepatitis B and C; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; CRP, C-reactive protein; TPO, thyroid peroxidase.

Treatment

The basic approach includes: (i) elimination or avoidance of the cause or trigger/stimulus, (ii) symptomatic pharmacological treatment by reducing mast cell mediator release and/or the effect of these mediators at the target organ and (iii) inducing tolerance.

Avoidance of Triggers or Stimuli

The elimination of triggers forms the backbone of management of urticaria in children. A comprehensive history covering all relevant exposures and triggers is a must. It has been depicted in **Figure 6**.

Specific Drug Therapy of Urticaria

The basic approach to drug therapy is outlined in **Figure 7**.

Second generation antihistamines These (cetirizine, levocetirizine) are now the recommended first-line therapy in management of urticaria in children. The dose can be increased up to fourfold (as per requirement) to achieve a control of the urticaria episode. Desloratadine, fexofenadine and loratadine are other effective and safe alternatives in children.

First generation antihistamines Despite the adverse effect profile and lack of satisfactory randomized control trials, first generation antihistamines are used in children owing to their extensive availability and experience amongst general practitioners. But, their use is not recommended in children less than 6 months.

Other therapies Montelukast is licensed for pediatric use, but there are very few studies assessing the effectiveness of adding montelukast systemic therapy to antihistamine treatment of urticaria in children. There is evidence to use cyclosporine, intravenous immunoglobulin (IVIG) or omalizumab in children.
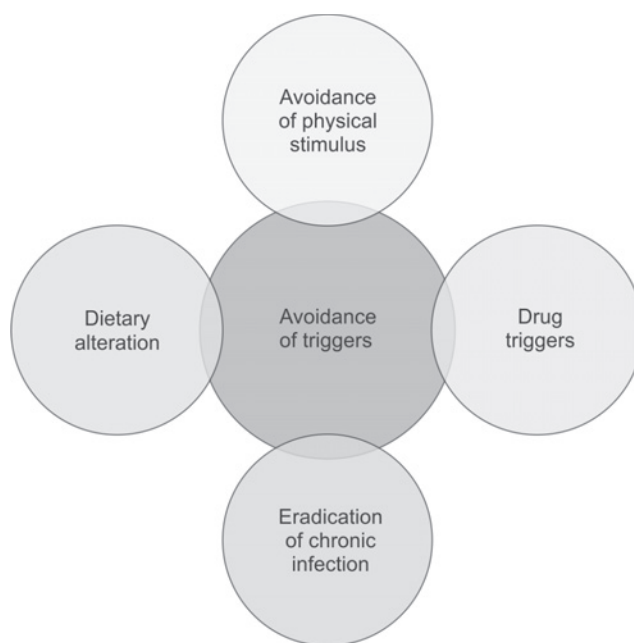
Figure 6 Avoidance of trigger is the integral part of management of urticaria
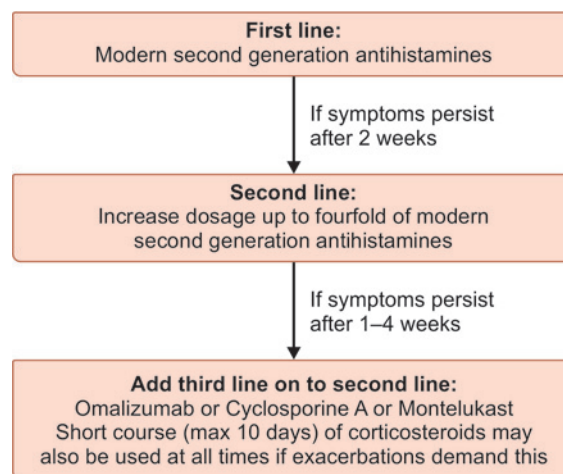
Figure 7 European Academy of Allergology and Clinical Immunology (EAACI) guidelines for management of urticaria

However, larger studies are required to support their use. Corticosteroids are useful to control acute episodes of extensive urticaria. However, due to the adverse side effect profile and abuse potential, their use should be limited. ASST has been useful diagnostic and therapeutic tool for management of chronic urticaria in adults. However, data of its use in children is limited.

Therapy of angioedema Patients with laryngeal edema should be closely monitored and endotracheal intubation or tracheostomy may be required. Intramuscular epinephrine should be given and it may be repeated after 10 min. Intravenous C1 inhibitors if available can be given for severe attacks with systemic involvement. Fresh frozen plasma is an alternative choice. Intravenous antihistaminics and steroids may be beneficial in allergic angioedema. Angiotensin II receptor antagonists should be avoided in patients of angioedema without urticaria.

MASTOCYTOSIS

Mastocytosis and its variants are characterized by a pathologic increase in mast cells in cutaneous tissue and extracutaneous organs such as the bone marrow, liver, spleen and lymph nodes. The disease presents in two primary age-related patterns: (i) pediatric-onset mastocytosis and (ii) adult-onset mastocytosis, which may differ in their clinical manifestations and disease course.

ETIOPATHOGENESIS

The release of mast cell mediators causes symptoms of flushing, itching and gastrointestinal disturbance in mastocytosis, but the reason for mast cell accumulation in tissues is not yet clear. The pathogenesis of cutaneous mastocytosis in children is not well understood and many children do not present with mutations of *c-kit* that codes for KIT, a membrane receptor for stem cell factor expressed in the surface membrane of mast cells which is found mutated in majority of the adult patients with systemic mastocytosis. KIT is also expressed on hemopoietic stem cells and melanocytes, which might be relevant to the occasional occurrence of myeloproliferative and myelodysplastic disorders in mastocytosis and the hyperpigmentation usually seen in urticaria pigmentosa lesions.

CLINICAL PRESENTATION

Pediatric-onset mastocytosis commonly is diagnosed prior to 2 years of age. The clinical presentation and the course of mastocytosis range from the more common cutaneous disease to the rare systemic forms **(Table 3)**.

Cutaneous Mastocytosis

Urticaria Pigmentosa

This is the most common pattern of cutaneous mastocytosis and most patients develop it within the 1st year of life. Numerous reddish-brown or pale maculopapules, plaques or nodules appear in a symmetrical distribution anywhere on the body except the face, head, palms and soles, with the highest concentration usually being on the trunk and thighs **(Fig. 8)**. They urticate within a few minutes of gentle rubbing (Darier sign). However, it is not always demonstrable and is not 100% specific for mastocytosis. Lesions may blister in infancy or childhood, but heal without scarring. Flushing occurs in about 50% of patients and other symptoms may include mild pruritus, heat or cold intolerance, recurrent diarrhea and headache.

Mastocytoma

Cutaneous mastocytosis may present with red, pink or yellowish nodules **(Fig. 9)** or plaques in infancy or early childhood. They are usually solitary. They tend to blister if rubbed which can also occasionally precipitate attacks of flushing. Nearly all mastocytomas involute over the 1st few years of childhood.

Telangiectasia Macularis Eruptiva Perstans

It is rare in pediatric age and presents with red, telangiectatic macules, especially on the trunk, which usually do not urticate on rubbing. Telangiectasia macularis eruptiva perstans tends to be very persistent and unresponsive to treatment.

Figure 8 Reddish-brown or pale maculopapules and plaques in a symmetrical distribution over the trunk in a patient of urticaria pigmentosa
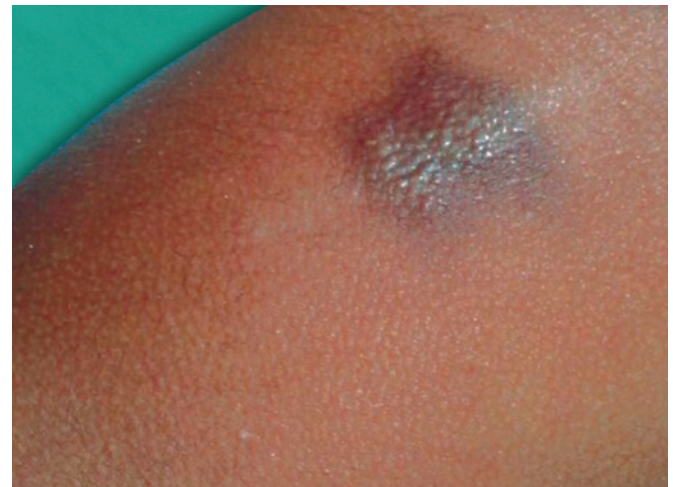
Figure 9 Hyperpigmented plaque with peau d'orange surface over left deltoid region

Table 3 Clinical classification of mastocytosis

Cutaneous	• Urticaria pigmentosa • Mastocytoma • Telangiectasia macularis eruptiva perstans • Diffuse cutaneous mastocytosis

Systemic (extracutaneous mast cells in at least one organ)	• Indolent systemic mastocytosis
	• Mastocytosis with an associated hematologic non-mast cell disorder (AHNMD)
	  – Myeloproliferative disorders
	  – Myelodysplastic disorders
	• Aggressive mastocytosis
	• Mast cell leukemia

Table 4 WHO criteria for diagnosis of systemic mastocytosis (2001)

Major	Multifocal dense aggregates of mast cells in bone marrow or other tissues (not skin)
Minor	1. On biopsy of bone marrow or other extracutaneous tissue ≥ 25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology OR ≥ 25% of mast cells on bone marrow aspirate are immature or atypical 2. Detection of a KIT point mutation at codon 816 in bone marrow, blood or other organs (not skin) 3. Mast cells in bone marrow, blood or other extracutaneous organs that coexpress CD117 with CD2 and/or CD25 4. Total blood tryptase persistently ≥ 20 ng/mL (unless there is an associated clonal myeloid disorder in which case this parameter is not valid)
Diagnosis	One major and one minor criteria or three minor criteria are fulfilled

Table 5 Treatment of pediatric mastocytosis

General measures	
Avoidance of triggers	Specific foods, medications, allergens and general triggers
Physical measures	Avoid sudden changes of temperature, avoid dryness of skin, avoid rubbing
Local care of skin	Use skin moisturizer, topical antibiotics (denuded lesions)
Specific measures	
Topical	Corticosteroid cream, water soluble sodium cromoglycate cream, and miltefosine
Systemic	H1 and H2 antihistaminics, sodium cromoglycate, antileukotrienes, proton pump inhibitors, corticosteroids, doxepin, epinephrine self injections, cytoreductive therapy with IFN-α, cladribine, cytarabine, fludarabine and hydroxyurea, imatinib, masitinib and bafetinib
Phototherapy	UVA (oral and bath psoralen UVA), narrow-band UVB

Abbreviations: IFN-α, alpha interferon; UVA, ultraviolet A; UVB; ultraviolet B.

Diffuse Cutaneous Mastocytosis

This is a rare form of mastocytosis in which mast cells infiltrate the entire skin diffusely and it usually presents in the neonatal period. The skin tends to be thickened and doughy in consistency, but may be smooth. Blistering after minor trauma or scratching is common and pruritus intense. The patients are at risk of systemic disease and severe complications including anaphylaxis. It may resolve spontaneously as in other types.

Systemic Mastocytosis

The WHO criteria for diagnosis of systemic mastocytosis are outlined in **Table 4**. Not all patients with proven bone marrow involvement will be symptomatic, but in those who have nausea, vomiting, diarrhea, palpitations, hypotension, syncope, headache, dyspnea, wheezing and sometimes fatigue and *fogginess* may feature dominantly as symptoms. Bone pain, bone cysts, premature osteoporosis, osteopetrosis or spontaneous fractures should prompt further investigation. Although there is a theoretical risk of progression of type I disease to type II or type III disease, this is unusual and that there are no markers to identify subgroups of patients at greatest risk of this. The occasional presentation of type III or type IV disease will be with the patient showing changes in the peripheral blood against a background of being unwell with lymphadenopathy.

INVESTIGATIONS

Skin Biopsy

There are increased numbers of mast cells in the dermis, especially perivascular and periappendageal. The epidermis is normal apart from an increase in melanin. The mast cells are usually oval or spindle-shaped and have granules that stain metachromatically with toluidine blue. Full-thickness infiltration of skin or a band like involvement of the upper dermis is seen in mastocytomas and diffuse cutaneous mastocytosis.

Bone Marrow

Bone marrow involvement typically presents with focal aggregates of mast cells on biopsy, although infiltration may be diffuse and spindle-shaped.

A suggested protocol for the initial diagnostic work-up and review is summarized in **Box 5**.

MANAGEMENT

Antihistamines are the mainstay of therapy. Itching and flushing can be controlled by H1-antihistamines in many patients, but can be refractory to treatment. H_2-antihistamines, proton pump inhibitors and sodium cromoglycate are used for persistent gastrointestinal symptoms. Aspirin and other NSAIDs have been reported to ameliorate prostaglandin-mediated flushing in some patients. Photochemotherapy with oral and bath psoralen ultraviolet A (PUVA) as well as narrow-band ultraviolet B (UVB) therapy may help itch and whealing, but the benefits are only temporary. Corticosteroids both topically as well as orally offer temporary symptomatic improvement for patients, especially those with aggressive systemic mastocytosis.

BOX 5 Diagnostic algorithm for children with mastocytosis

- History (the onset and duration of the disease, provoking factors, presence of mediator-related symptoms and anaphylaxis, mastocytosis in family)
- Physical examination (inspection of the skin, Darier sign, organomegaly: liver, spleen, lymph nodes)
- Skin biopsy, blood chemistry, serum tryptase levels, bone marrow biopsy*, flow cytometric analysis of bone marrow* and determination of KIT mutation (D816V)*.

To be done when serum tryptase levels > 20 ng/mL or rising, or associated with clinically significant abnormalities in the peripheral blood; or organomegaly (liver, spleen or lymph nodes)

A suggested protocol for the treatment is summarized in **Table 5**. Despite recent advances in understanding the pathophysiology of mastocytosis, no standard treatment exists and there are no predictors for the onset of hematological complications or occurrence of familial disease. Independent of the disease variant, all patients require avoidance of factors triggering mediator release and symptomatic therapy to control mediator-related symptoms. Patients should be advised about the possibility of an anaphylactic emergency and should carry an epinephrine pen for self-administration when needed.

PROGNOSIS

Most pediatric patients with cutaneous or indolent systemic mastocytosis will have an excellent prognosis. Most mastocytomas resolve in childhood. The outlook for pediatric cases that does not remit is the same as for adults with indolent disease and progression to significant hematological disorders is rare. The main problems likely to be experienced by patients relate to the risks of anaphylaxis and peptic ulceration. Prognosis of aggressive mastocytosis will relate to the associated hematological disorder.

MORE ON THIS TOPIC

Caffarelli C, Cuomo B, Cardinale F, et al. Aetiological factors associated with chronic urticaria in children: a systematic review. Acta Derm Venereol. 2013;93:268-72.

Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. Expert Opin Pharmacother. 2013;14:2033-45.

Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, et al. The natural history of chronic urticaria in childhood: a prospective study. J Am Acad Dermatol. 2014;71: 663-8.

Frieri M, Quershi M. Pediatric mastocytosis: a review of the literature. Pediatr Allergy Immunol Pulmonol. 2013;26:175-80.

Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. Pediatr Allergy Immunol. 2008;19:363-6.

Pite H, Wedi B, Borrego LM, et al. Management of childhood urticaria: current knowledge and practical recommendations. Acta Derm Venereol. 2013; 93:500-8.

Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69:868-87.

Chapter 48.9
Cutaneous Drug Reactions
Rajib Malakar, Sandipan Dhar

An adverse drug reaction is defined by the World Health Organization (WHO) as *"a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function."* In this chapter, we shall discuss those adverse drug reactions that manifest with a skin lesion. Adverse cutaneous drug reactions (ACDR) vary from mild to severe forms. They encompass a full spectrum from localized skin involvement to more widespread systemic conditions. The immunology of severe reactions is not very clearly documented though role of T-cell mediation is thought to play the pivotal role. The limitation of laboratory testing for drug hypersensitivity makes clinical observation the mainstay, especially when the subject is on multiple drugs.

CLASSIFICATION

Adverse cutaneous drug reactions can be divided into different classes based on pathogenesis and clinical be morphology. On the basis of dose relation and predictability, there can be type A (augmented) which is on account of excessive pharmacological effects despite dosage being within therapeutic range and type B (bizarre) which is unpredictable and is not at all dependent on dosage or pharmacological effects. Another classification for regular clinical usage divides them into immediate and nonimmediate reactions (NIRs), accelerated or delayed type reactions. The immediate type manifests in an hour's time manifesting as angioedema or anaphylaxis. NIRs manifest by hours, days or even weeks of taking the drug.

Immune versus Nonimmune Reactions
- *Nonimmune cutaneous reactions:* These include photosensitivity eruptions, pigmentation changes, warfarin necrosis of skin and simple pruritus.
- *Immune cutaneous reactions:* These are more common. These may present as maculopapular eruptions, urticaria, angioedema, or fixed drug eruptions. Severe varieties include vasculitis; pustular eruptions: acute generalized exanthematous pustulosis (AGEP); hypersensitivity syndrome: drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

DoTS Classification
Drugs reactions can also be divided considering dose relatedness, timing and patient susceptibility (DoTS). Dose relatedness points to the doses above, below, or within the common therapeutic range (toxic, hypersusceptibility and collateral adverse reactions). The significance of time relatedness considers time between first use and the appearance of the adverse reaction and hence is: immediate, first dose, early, intermediate, late and delayed. The role of susceptibility factors consider several factors that enhance the susceptibility to the adverse reaction like genetic, age, gender, physiological changes, exogenous drugs and diseases.

EPIDEMIOLOGY

Adverse cutaneous drug reactions are now quite common and some can be lethal and life-threatening. Reactions to different drugs affect almost about 3% of patients admitted in hospitals. Reaction rates from different studies show a range from 0 to 8% and are more for nonsteroidal anti-inflammatory drugs (NSAIDs) and antimicrobials such as amoxicillin (5.1%), ampicillin (4.5%) and cotrimoxazole (3.7%). The most common skin presentation is morbilliform rash (91%) and urticaria (6%). Severe reactions occur in about 1 in 10,000 to 1 in 1 million users: SJS and TEN. Sulfonamide antibiotics, allopurinol, phenytoin and carbamazepine are commonly implicated for these severe reactions.

Common drugs found to cause cutaneous reactions in a study by Marfatia were NSAIDs (21%) followed by the sulfa group (14%) whereas Pudukadan et al. reported cotrimoxazole (22.25%) followed by dapsone (17.7%) as the most common offenders. In HIV-infected persons, trimethoprim-sulfamethoxazole causes severe reactions in up to 40% of patients when used in higher doses. Anti-HIV medications were frequently associated with greater than or equal to 10% drug eruptions. The risk of reaction increases with the number of drugs taken, age of the patient and viral infections. Patients at risk are those with transplants, HIV infection and those suffering from collagen vascular diseases. Drugs with higher molecular weight and structural complexity are likely to produce a higher incidence of drug reactions. Genetic ability of an individual to detoxify toxic metabolites predisposes to the development of drug reaction. Human leukocyte antigen (HLA) genes *HLA-B*1502* predispose to carbamazepine-associated SJS and TEN and *HLA-B*5701* to abacavir hypersensitivity syndrome.

PATHOGENESIS

The mechanism of action is unknown in most cases. The adverse reaction can be mediated by immunologic and nonimmunologic mechanisms. The reactions which are immunologic (Coombs and Gell) need a host response resulting from IgE-dependent, immune complex-initiated, cytotoxic or cellular immune mechanisms. The nonimmunologic reactions may be initiated by nonimmunologic pathways, idiosyncrasy (pharmacogenetic), cumulative toxic effects and drug interactions. Reactions on account of non-immunological mechanism are more common.

Gell and Coombs Classification of Immunological Reactions
- *Type I: Acute IgE-mediated reactions:* That cause mast cell degranulation like anaphylactic and urticarial reactions.
- *Type II*: *Cytotoxic reactions*, due to antigen-antibody interactions leading to production of anaphylotoxin (C5a), polymorphonuclear leukocytes aggregation and tissue injury by hydrolytic neutrophil enzymes as in vasculitis.
- *Type III*: *Delayed immune complex reactions*, where in antigen-antibody complexes are produced and accumulate in tissues as in maculopapular lesions.
- *Type IV*: *Cell-mediated or delayed hypersensitivity* reactions where T-lymphocyte sensitization is brought about by a hapten-protein complex as in contact dermatitis.

Nonimmunologic Reactions
Urticaria, photosensitivity eruptions, erythema multiforme, pigmentation, morbilliform reactions, fixed drug reactions, TEN and bullous reactions are some of the clinical manifestations.

Nonimmunologic activation of effector pathways is also an important mechanism. Drugs release mediators from mast cells and precipitate anaphylaxis or urticaria. Some drugs may activate complement in absence of antibody. Phototoxicity starts when the drug or chromophore absorbs radiation to elicit a reaction.

Commonly offending drugs are variable in diverse ethnic populations. SJS and TEN are mostly found to be precipitated by NSAIDs and sulfonamides in the Western literature whereas carbamazepine is found to be the major implicated agent for SJS in South-East Asia. Studies now point to an association between HLA alleles and hypersensitivity to several drugs including nevirapine, allopurinol and carbamazepine. Considering the linkage of *HLA-B*1502* and carbamazepine, *HLA-B*1502* allele was found in 100% of people with carbamazepine-induced SJS or toxic epidermal necrolysis, and only 3% of carbamazepine-tolerant people in a study from Taiwan. The same was further substantiated in cohort of Chinese descent originating from different geographic regions. This association was not found among people with European descent. The allele is ethnically relevant. Found in 5–13% of South-East Asians compared to 0–1% in Europeans.

Stevens-Johnson syndrome and its association with HLA-B molecules indicate an obvious role in its causation. This presents the drug to CD8 cells resulting in clonal expansion of CD8 cytotoxic lymphocytes. This cytotoxic effector response leads to apoptosis of keratinocytes. These pathways are not specific to overlapping SJS and toxic epidermal necrolysis. Chung found that granulysin, a cytolytic protein from CD8 cells, occurs in blister fluid in significant levels and correlates disease activity.

CLINICAL PRESENTATIONS

In serious drug-induced cutaneous eruptions, erythema, urticaria, skin necrosis Blisters, positive Nikolsky's sign have been observed. Some general symptoms like fever, lymphadenopathy and joint pains may also occur. The nonimmune cutaneous reactions include photosensitivity from fluoroquinolones and cycline antibiotics, pigmentary changes from oral contraceptives, minocycline. Necrosis of skin occurs between the 3rd and 10th days of warfarin initiation. Nonscarring alopecia is often noted with antineoplastic agents. The target organ commonly involved in NIRs is the skin where there is a wide spectrum of manifestations like maculopapular exanthema (MPE), urticaria, acute generalized exanthematic pustulosis (AGEP), DRESS or drug-induced hypersensitivity syndrome (DIHS), SJS, TEN, erythema multiforme (EM) and fixed drug eruption.

NIRs are mainly less severe diseases like exanthematic reactions and MPE, and urticaria. Severe forms like DRESS or DIHS and bullous reactions with mucosal involvement are often noted. Erythema multiforme, mostly of viral etiology presents with target lesions. The most severe are SJS and TEN characterized by widespread epidermal detachment and mucosal erosion and are mainly due to a drug etiology.

A study has suggested that a new variety of lesion occurs in addition to EM, SJS and TEN, namely *flat typical target*. The classical lesions are the raised type target lesions.

DIAGNOSIS

The drug history forms the cornerstone in the diagnosis and allergology examination and tests further substantiate it. Prick, intradermal and patch tests are the common forms of allergy tests. Specific IgE level is a popular in vitro method for immediate reaction detection. Basophil activation test and lymphocyte proliferation assays also add to the investigation basket. Some cases need drug provocation tests for a complete work-up. Patients having severe drug reaction like TEN are not subjected to drug challenge for the risk serious outcomes.

The laboratory findings in serious drug-induced cutaneous eruptions are: eosinophil count greater than 1,000/μL, lymphocytosis with atypical lymphocytes and abnormal liver function test results. Tests for IgE are available for the drugs like penicillins, cephalosporins, peptide and protein drugs (insulin). In some patients, such as antiretroviral therapy in AIDS, the need for HLA typing before initiating abacavir is routinely recommended.

Immunohistochemistry Skin biopsy from the acute reaction site with immunohistochemistry data helps in the investigation of the immunologic mechanisms involved and not the drug involved. Mononuclear cell infiltrate composed mainly of activated T-cells expressing DR antigens, CD69 activation markers is an usual finding.

MANAGEMENT

Suspected agents should be immediately withdrawn and not repeated although the risk-benefit ratio needs to be evaluated in case of necessary medicines. Symptomatic management is usually required. Calamine lotion or oral antihistamines usually relieve pruritus and topical corticosteroids reduce inflammation and itching. Systemic corticosteroids are needed for more severe reactions.

Commonly drug eruptions are reversible; abating spontaneously after the offending drug is withdrawn. The drug half-lives serve as a guide to resolution, as with long half-lives, the time to resolute may be much longer.

The fact that SJS and TEN are due to dermal cell apoptosis, intravenous immunoglobulin is advocated to block apoptosis via the Fas pathway. Studies on the use of intravenous immunoglobulin in TEN have reported good results. A study of 10 consecutive patients with TEN of moderate severity was treated with different doses of intravenous immunoglobulin (IVIG) (0.2–0.75 g/kg of body weight per day for 4 consecutive days); there was recovery in all cases. Blood transfusion in cases of SJS and TEN helps in many ways as— toxic metabolites, cytotoxic T-cells and autoantibodies get diluted by hemotransfusion; as well as supplies immunoglobulins to fight infections. A benefit of plasmapheresis for treatment of TEN or SJS is also reported. Cyclophosphamide was also claimed to produce good results. A retrospective comparative study showed cyclosporine was safe and produced good re-epithelialization rate and a lower mortality. Tumor necrosis factor is a mediator of cell death in toxic epidermal necrolysis, and control of the progression of TEN with intravenous anti-tumor necrosis factor antibody infliximab yielded better outcomes.

EDUCATION

When the responsible drug is pinpointed, it is prudent to avoid that drug later on by the patient. The patients are instructed to carry a record of the drugs to which they have allergies or had a severe drug reaction. Drugs that are cross-reactive have also to be notified to the patient and avoided. Penicillin allergic patients often have cross-reactivity with cephalosporins group, and sulfonamide allergic subjects cross-react with other sulfa group drugs. These facts are to be particularly emphasized when the parents are counseled.

MORE ON THIS TOPIC

Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. Br J Clin Pharmacol. 2011;71:672-83.

Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ. 2003;327:1222-5

Coombs PR, Gell PG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR. Clinical Aspects of Immunology. Oxford: Oxford University Press; 1968. pp. 575-96.

Ghosh K, Banerjee G, Ghosal AK, Nandi J. Cutaneous drug hypersensitivity: immunological and genetic perspective. Indian J Dermatol. 2011;56:137-44.

Hotchandani SC, Bhatt JD, Shah MK. A prospective analysis of drug-induced acute cutaneous reactions reported in patients at a tertiary care hospital. Indian J Pharmacol. 2010;42:118-9.

Nayak S, Acharjya B. Adverse cutaneous drug reaction. Indian J Dermatol. 2008;53:2-8.

Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol. 2008;74:430.

Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care centre in South India. Indian J Dermatol Venereol Leprol. 2004;70:20-4.

Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM. Textbook of Adverse Drug Reactions. Oxford: Oxford University Press; 1977. p.10.

Romano A, Blanca M, Torres MJ, et al. Diagnosis of nonimmediate reactions to beta-lactams antibiotics. Allergy 2004;59:1153-60.

Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruptions among children and adolescents in north India. Pediatr Dermatol. 1995;12:178-83.

Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71:684-700.

Torres MJ, Mayorga C, Blanca M. Nonimmediate allergic reactions induced by drugs: pathogenesis and diagnostic tests. J Investig Allergol Clin Immunol. 2009;19:80-90.

Ueta M, Sotozono C, Inatomi T, et al. Association of Fas Ligand gene polymorphism with Stevens-Johnson syndrome. Br J Ophthalmol. 2008;92:989-91.

Chapter 48.10
Cutaneous Manifestations of Nutritional Deficiency Diseases
Vibhu Mendiratta

Consumption of quantitatively insufficient or qualitatively poor diet can cause multiple nutritional deficiencies. Nutritional deficiency states have recognizable skin manifestations which offer early clues for diagnosis of the underlying disease, thus curtailing related morbidity and mortality. This chapter highlights skin manifestations of some common nutritional deficiency states in children.

PROTEIN ENERGY MALNUTRITION (PEM)

There is generalized edema **(Fig. 1)**, pot belly appearance, irritability and failure to thrive. Skin shows brownish discoloration and scaling over trunk and extremities. Legs, buttocks, trunk and pressure areas develop fissures and erosions along with patches of dry/shiny scaly skin known as *crazy pavement dermatosis* or flaky paint dermatosis **(Fig. 2)**. Hairs over the frontal scalp are sparse, thin and light colored (brownish-yellow hue), which alternate with light colored hair that correspond with periods of malnutrition giving rise to a band (the *Flag sign*) **(Fig. 3)**. Skin changes mimic atopic dermatitis, *ichthyosis*, epidermolysis bullosa, staphylococcal scalded skin syndrome and cystic fibrosis.

Marasmus

Child appears apathetic and old due to loss of buccal pad of fat. Skin is cool, dry and wrinkled with extreme wasting of subcutaneous fat **(Fig. 4)**. Hairs are sparse, fine and brittle. Angular cheilitis and atrophic tongue may be associated. Fissured and dry skin is treated with emollients like paraffin and/coconut oil. Topical antibacterial agent is added in the presence of secondary infection.

Noma

Noma is considered an opportunistic disease arising from a complex interaction between anaerobic infection and severe undernutrition seen predominantly in small children (< 4 years). Famine, human immunodeficiency virus infection and immunocompromised states predispose to noma. Nodulo-ulcerative lesion develops commonly over cheek first which later ulcerates along with soft tissue necrosis. Necrosis extends into the oral cavity and involves its soft tissue muscle and bone in an irregular pattern. The oral cavity and cheek may be completely destroyed with mutilation.

Figure 1 Facial edema with shiny, brown skin in kwashiorkor

Figure 2 Peeling of skin with desquamation at frictional areas

Figure 3 Flag sign in kwashiorkor

Figure 4 Marasmic child (Loss of subcutaneous fat, wrinkling and old man facies in marasmus)

Extensive ulceration with loss of soft tissue resembles pyoderma gangrenosum and tubercular ulcers. Management includes control of infection with appropriate antimicrobials effective against gram-positive and anaerobic bacteria, correction of the underlying malnutrition and reconstructive facial surgery.

Phrynoderma

Phrynoderma was originally described in association with vitamin A deficiency and ocular signs, but is now known to occur in association with other nutritional deficiencies of essential fatty acids and vitamin E. Consumption of diet low in essential fatty acids leads to dry, scaly skin. Presence of multiple grayish-black, hyperkeratotic follicular papules is noted mainly around elbows, knees, thighs and buttocks. Diet containing essential fatty acids, vitamin A and E is recommended with application of emollients like paraffin, shea butter topically.

VITAMIN DEFICIENCIES

- *Vitamin A:* Skin is dry, rough and scaly. Hairs are brittle and thin. Grayish, keratotic grouped follicular papules may be seen located over extensor surfaces of knees, elbows, and buttocks.
- *Vitamin B2 (riboflavin)*: Deficiency of vitamin B_2 causes cheilitis, glossitis, seborrheic dermatitis and scrotal dermatitis. Occasionally, keratitis and conjunctivitis may be seen. Oral supplementation of riboflavin in a dose of 3–10 mg reverses mild changes.
- *Vitamin B3 (niacin):* Skin changes first appear over sun exposed areas (face, extensor surface of arms, hands and *V* area of neck in the form of erythema, hyperpigmentation and scaling strictly in the photo exposed area **(Fig. 5)**. It is easily confused with photodermatitis. Later skin turns brown rough, hyperkeratotic and scaly. Dorsal hand involvement with presence of hyperpigmented, scaly, erythematous skin **(Fig. 6)** and like a collar around the neck (Casal's necklace) is a characteristic feature. Diarrhea, mental irritability, depression and anxiety often accompany cutaneous changes. Cheilitis and glossitis may also be noted. Supplementing niacin orally (300 mg/day) or 100 mg of niacin intravenously along with a balanced diet reverses skin and mental changes.
- *Vitamin B₆ (pyridoxine):* Deficiency can cause seborrhea like changes, cheilitis, glossitis and conjunctivitis.

- *Vitamin B₁₂ (cyanocobalamin) and folic acid:* Glossodynia, angular cheilitis, erythematous mucositis, stomatodynia and recurrent aphthae are seen early. Pigmentary changes vary from deep brown or brownish-black pigmentation affecting the hands and feet with dorsal fingers and toes displaying the most pronounced pigmentation **(Fig. 7)**. Accentuation over the interphalangeal joints and the terminal phalanges is common. Nails are generally spared but may show longitudinal pigmented bands. Diffuse, addisonian pigmentation and mucosal pigmentation **(Fig. 8)** may be encountered.
- *Biotin (vitamin H):* Periorificial dermatitis is a salient finding. There may be pallor of skin and hair. Diffuse alopecia, glossitis are prominent **(Fig. 9)**. Seizures and erythroderma are noted in severe deficiency. Milder deficiency resembles acrodermatitis enteropathica and shows scaly, crusted plaques around oral cavity. Oral supplementation with 10–30 mg biotin can reverse the changes.
- *Vitamin C:* Deficiency of vitamin C results in follicular keratotic papules with perifollicular hemorrhages. Ecchymoses, painful bluish gum swelling and bleeds in children aged 6–24 months are common manifestations. Rosary nodules can be palpated at the costochondral junctions. Vitamin C (150 mg/day) reverses changes.

OTHER DEFICIENCIES

- *Acrodermatitis enteropathica (zinc deficiency):* Only 20% of patients will manifest all three of the signature findings at presentation, i.e., acral dermatitis, diarrhea and alopecia. Periorificial and acral rash are eary signs **(Fig. 10)**. Onychodystrophy, paronychia, blepharitis and conjunctivitis may additionally be seen. Child is irritable. Symptoms appear around weaning of the infant as periorificial erythema, scaly plaques and erosions along with cheilitis, glossitis with superimposed candidiasis. Hair are dull, brittle and light colored. Nails become dystrophic. Zinc supplementation either as zinc gluconate or sulphate produces dramatic reversal of symptoms within 48–72 hours and serves as a therapeutic diagnosis.
- *Copper deficiency:* Menkes syndrome is X-linked recessive disorder that is characterized by low copper levels. Cutaneous features appear at 2–3 months as fragile kinky hair, pale skin, pili torti. There is lethargy, hypotonia, seizures, mental retardation

Figure 5 Photosensitive rash of pellagra

Figure 6 Erythema, hyperpigmentation and desquamation over extensor surfaces of arm in pellagra

Figure 7 Hyperpigmentation of hands and nails

Figure 9 Sparse scalp hair in biotinidase deficiency
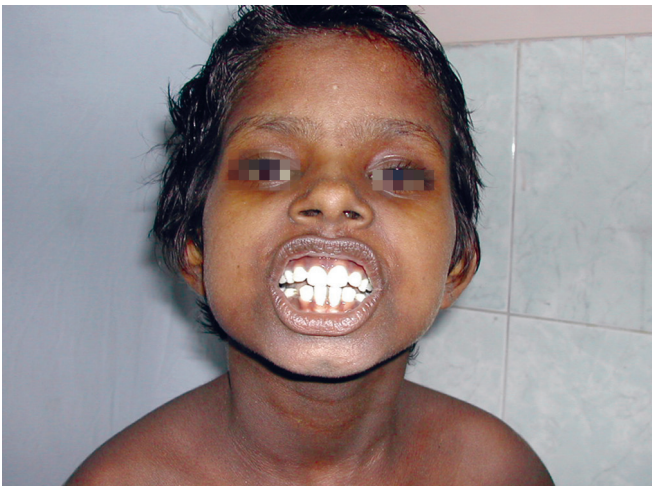
Figure 8 Oral pigmentation and facial darkening in vitamin B$_{12}$ deficiency

Figure 10 Periocular and perioral desquamation and post-inflammatory hypopigmentation in acrodermatitis enteropathica

and failure to thrive. Parenteral administration of copper and ceruloplasmin constitute the mainstay of treatment.

- *Selenium deficiency:* Deficiency of selenium results in skin hypopigmentation and color dilution of hair, nails and muscle weakness. A recent report by Kanekura et al., described an 18-month-old boy receiving parenteral nutrition resulting in selenium deficiency that led to cardiomyopathy as well as xerosis, erythematous scaly papules and plaques on the cheeks, hips, thighs and popliteal areas as well as erosions in the diaper area. Cheilitis and sparse light-colored hair were also noted.

MORE ON THIS TOPIC

Bates CJ. Vitamin A. Lancet. 1995;345:31-5.

Heath ML, Sidbury R. Cutaneous manifestations of nutritional deficiency. Curr Opin Pediatr. 2006;18:417-22.

Miller SJ. Nutritional deficiency and the skin. J Am Acad Dermatol. 1989;21:1-30.

Ruiz-Maldonado R. Cutaneous manifestations of malnutrition and trace element deficiencies. In: Caputo R, Gelmetti C. Proceedings of the 5th International Congress of Pediatric Dermatology. Milan:Cilay-Pharma; 1989.

Chapter 48.11
Cutaneous Manifestations of Collagen Vascular Diseases
Yogesh S Marfatia

Many rheumatologic diseases manifest with distinct clinical presentations on the skin. Collagen vascular diseases have in common inflammatory tissue damage, tendency to chronicity with acute exacerbations, response to high doses of systemic corticosteroids and/or immunosuppressive agents. Their heterogeneity translates into a wide range of clinical presentations. Since there are specific correlations between cutaneous manifestations, autoantibody profiles and disease course, the skin has an important marker function, both for the diagnosis and prognosis, as it is easily accessible both to physical examination and biopsy.

JUVENILE DERMATOMYOSITIS

Dermatomyositis, an inflammatory vasculopathy primarily affecting muscle and skin; when occurs before 18 years of age, is designated as juvenile dermatomyositis (JDM). It is a rare, serious autoimmune condition of childhood which typically affects skin and muscle, but can also involve the joints, gut, lung, heart and other internal organs. It is the most common idiopathic inflammatory myopathy of childhood, more common in girls than in boys, by a ratio of approximately 2.3:1. Children with a genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB *0301) might have prolonged exposure to maternal chimeric cells/ unknown environmental triggers which activate a cascade through interferon I. Approximately 30% of children present with rapid appearance of rash, weakness and pain. Another 50% have insidious development of muscle pain and progressive weakness associated with rash. The remaining cases present with a subacute onset of skin rash preceding appearance of muscular symptoms.

*Heliotrope rash (**Fig. 1**)* It is a pruritic, symmetrical, bluish-violet erythema usually seen on upper eyelids, upper cheeks, forehead and temples. It is the only skin sign paralleling clinical course.

Shawl sign There is extreme photosensitivity to UV light exposure causing erythema in exposed areas (chest and back).

*Gottron's papules (**Fig. 2**)* They are bright pink, shiny thickened atrophic plaques seen on proximal and distal interphalangeal joints.

Mechanic's hands They are seen due to hyperkeratosis and peeling of the skin over the lateral and palmar aspects of the fingers.

Calcinosis It is characterized by dystrophic deposition of calcium salts in subcutaneous nodules leading to painful ulceration of skin with extrusion of crystals.

Figure 1 Juvenile dermatomyositis: Heliotrope rash

Figure 2 Juvenile dermatomyositis: Gottron's papules

Other features Lipodystrophy may be present. Small vessel inflammation in nail folds and gums is seen as thickened, tortuous or absent capillary loops. There is presence of cutaneous ulcers on toes, fingers, axillae and epicanthal folds. Telangiectasias, if present are seen with capillaroscopy.

Specific treatment is described in detail in Section 46. Supportive therapy includes photoprotective measures, calcium and vitamin D supplementation, active and passive physiotherapy. Calcinosis can be treated with diltiazem, aluminum hydroxide, bisphosphonates, intralesional corticosteroid, curettage, surgical excision, CO_2 laser and extracorporeal shock wave lithotripsy.

JUVENILE SLE

It is an autoimmune disorder characterized by inflammatory damage to joints, kidney, central nervous system, and hematopoietic system. Skin cells in systemic lupus erythematosus (SLE) have increased susceptibility to damage from UV light. The apoptotic cells release nucleic acid antigens and autoantibodies are formed against them. There is deposition of immune complexes in tissues leading to proinflammatory cascade and tissue damage.

Discoid Lupus Erythematosus
Discoid lupus erythematosus (DLE) lesions can be present in absence of serologic and clinical evidence of systemic disease and can also be seen as a part of cutaneous manifestations of SLE. It is less frequent in pediatric age group. *Discoid rash* is characterized by plaques with adherent keratotic scaling, follicular plugging, pigmentary changes, telangiectasia and atrophy. If not treated early has a potential for scarring and disfigurement. It is also known as chronic cutaneous lupus erythematosus.

Subacute Cutaneous Lupus Erythematosus
Childhood SLE cases may have an urticaria-like or a papulosquamous malar dermatitis primarily on sun exposed areas and is known as subacute cutaneous lupus erythematosus. Such cases have lesser systemic involvement and are often anti-Ro positive.

Systemic Lupus Erythematosus
Malar rash **(Fig. 3)** is characterized by fixed erythema, over the malar eminences, tending to spare the nasolabial folds. Photosensitivity is invariably present. Vascular features include vasculitic macular eruptions on distal extremities and in the subungual region, with visible microinfarcts from small vessel vasculitis,

Figure 3 Juvenile SLE: Malar rash

Figure 4 *Morphea:* Plaque type

purpura and livedo reticularis *Raynaud phenomenon* may be present. Oral ulcers tend to be present on palate, buccal mucosa and tongue and are usually painless. Ulcers may even be present on nasal mucosa. Nonscarring alopecia characterized by diffuse thinning or hair fragility with visible broken hairs may be seen.

Topical Therapy

Moderately potent topical or intralesional steroids are the first line therapy for localized lesions of DLE. Topical tacrolimus (0.1%) is found to be effective. In contrast to topical steroid, it can be used for a longer duration without side-effects like atrophy and pigmentary changes. Corticosteroids are the mainstay of systemic therapy. Details of treatment are provided in Section 46.

Neonatal Lupus Erythematosus (NLE)

It is one of the few rheumatic disorders manifesting in the neonate resulting from passive transfer of maternal IgG autoantibodies (mostly including anti-Ro and anti-La) to the fetus. The clinical spectrum includes cutaneous manifestations, congenital heart block, and cytopenias. Cutaneous manifestations consist of annular or macular rash affecting the face particularly the periorbital area, trunk and scalp is characteristic. It is seen within first 6 weeks of life after exposure to UV light and lasts for 3–4 months. Telangiectasia is often prominent. Atrophic telangiectatic changes are most evident near the temples and scalp. Photoprotection and low potency topical corticosteroids are the mainstay of therapy for cutaneous lesions of NLE. Parents of the affected children must be thoroughly counseled regarding avoidance of sunlight, proper use of sunscreen, and protective clothing. Sometimes, though there is resolution of active skin lesions, pigmentary changes, atrophy, and telangiectasia may persist over face and other exposed body parts. In such cases cosmetic camouflage helps these children in social interaction. Persistent telangiectasia may be managed with vascular LASER. In rare cases, if systemic therapy is indicated, hydroxychloroquine may be used.

JUVENILE SCLERODERMA

It constitutes various conditions which have fibrosis of skin as a common feature. The hallmark of scleroderma is thickening and hardening of skin (hidebound skin), which may take several years to develop. It is divided into: *localized scleroderma* (morphea-limited to skin) which is more common and *systemic scleroderma*
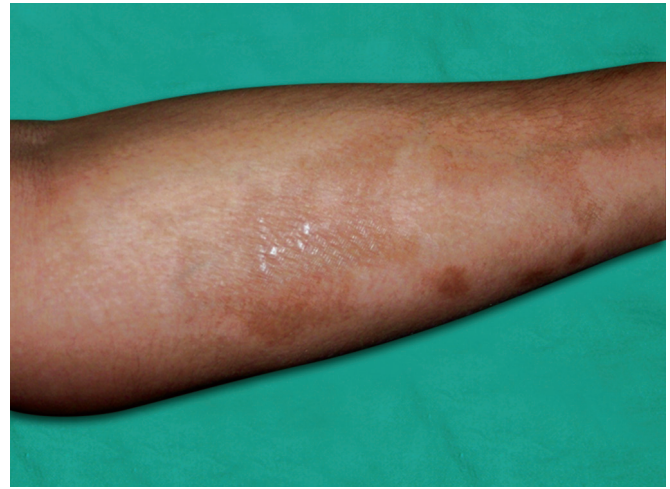
(systemic sclerosis) with organ involvement. Autoimmunity, vasculopathy, immune activation and fibrosis are main factors implicated in the pathogenesis.

Morphea (Localized Scleroderma)

Plaque Morphea (Fig. 4)

It is a unilateral, indurated, circumscribed, circular, ivory-colored area with a violaceous halo (lilac ring) usually confined to dermis. Topical tacrolimus ointment (0.1%) is the first line of treatment for limited plaque morphea. In absence of response after 8 weeks, modalities like lesional phototherapy, according to availability (NB-UVB/PUVA/UVA/UVA1), topical calcipotriol under occlusion, topical imiquimod or topical calcipotriol with betamethasone dipropionate may be used.

Generalized Morphea

Coalescence of morphea plaques in three or more anatomic sites constitutes generalized morphea. It is usually bilateral and involves the dermis. Generalized morphea without joint contracture is treated with phototherapy. It is preferred over methotrexate as first line of treatment. If there is no response after 8 weeks of phototherapy, combination therapy of systemic corticosteroid, and methotrexate is administered. If the patient does not respond in further 8 weeks, mycophenolate mofetil has to be started. Vitamin D and its analogues (calcitriol) have been used and found to be beneficial in some cases. Emollients can be used for xerosis caused by destruction of sweat glands. Active physical therapy is advocated to prevent contractures.

Linear Morphea

It is characterized by linear lesions extending through the dermis, subcutaneous tissue, muscle up to underlying bone. It is mostly unilateral. It may involve limbs or trunk **(Figs 5 and 6)** as linear streaks or manifest as *en coup de sabre* or Parry-Romberg syndrome.

En coup de sabre (cut of the sword Fig. 7) It is a linear atrophic depressed groove usually on frontoparietal region which if extends up to the scalp may cause cicatricial alopecia. It may extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headache. *Parry-Romberg syndrome* is characterized by hemifacial atrophy without a clearly definable en coup de sabre lesion.

Figure 5 *Morphea:* Linear type with atrophic changes
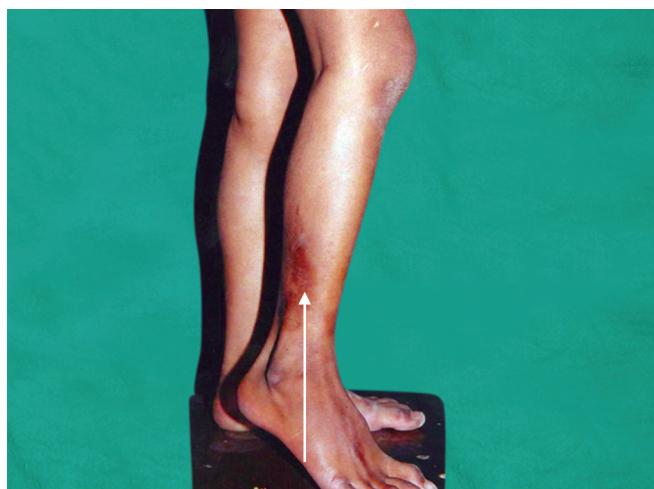
Figure 6 *Morphea:* Linear type with atrophic changes

Figure 7 *Morphea: En coup de sabre*

Figure 8 *Juvenile systemic sclerosis:* Diffuse salt and pepper appearance

Neurologic involvement may be present. Combination of methotrexate and systemic steroid remains the first therapeutic choice especially in linear and deeper subtypes having significant risk of disability. In absence of response after 8 weeks, modalities like lesional phototherapy, according to availability (NB-UVB/PUVA/UVA/UVA1) and mycophenolate mofetil may be used.

Deep Morphea
Deeper layers, including panniculus, fascia, and muscle are involved. It is mostly bilateral.

Disabling Pansclerotic Morphea of Childhood
There is generalized full-thickness involvement of skin on the trunk, face and extremities. Finger tips and toes are also involved.

Juvenile Systemic Sclerosis (JSS)
This can be categorized as diffuse or limited. The diffuse variant is more common in children. The skin involvement extends above the elbows and knees. Symmetric thickening and hardening of skin with fibrous and degenerative changes of viscera is present **(Figs 8 and 9)**. Limited variant is rare in childhood. It is defined

Figure 9A *Juvenile systemic sclerosis:* Cicatricial alopecia

Figure 9B *Juvenile systemic sclerosis:* Diffuse

Figure 9C *Juvenile systemic sclerosis:* Diffuse

as skin involvement confined to areas distal to the elbows and knees. It was previously known as CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome. Systemic sclerosis is discussed in detail in Section 46.

MORE ON THIS TOPIC

Cahill J, Sinclair R. Cutaneous manifestations of systemic disease. Aust Fam Physician. 2005;34:335-40.

Callen JP. Dermatomyositis. Lancet. 2000;355:53-7.

Gane NF. A guide to bullous lesions of the skin. J Clin Pathol. 1973;26(3):235-7.

Hurwitz S. The skin and systemic disease in children. Curr Probl Pediatr. 1977;7:1-68.

Lovell CR. The skin and systemic disease. Nursing (Lond). 1983;2:277-9.

Magro CM, Crowson AN. The spectrum of cutaneous lesions in rheumatoid arthritis: a clinical and pathological study of 43 patients. J Cutan Pathol. 2003;30:1-10.

McDonald CJ. Cutaneous manifestations of systemic disease. Postgrad Med. 1981;69:132-5, 138-40.

Chapter 48.12
Neurocutaneous Syndromes

Resham J Vasani

The term neurocutaneous syndromes generally refer to an increasingly large group of heterogeneous disorders that have in common both skin and nervous system. These are generally familial disorders with defect in the differentiation of the primitive ectoderm. This organization helps to identify and anticipate neurological complications in patients who have readily identifiable skin abnormalities. The disorders commonly identified as neurocutaneous syndromes are included in **Box 1**. Most of these disorders have been already discussed in detail in Chapter 42.6 on neurocutaneous syndromes. In this chapter, we will discuss the cutaneous manifestations of these disorders. Readers should refer to Section 42 for discussion on other aspects of these disorders.

BOX 1 Neurocutaneous syndromes

- Neurofibromatosis I and II
- Tuberous sclerosis
- Von Hippel-Lindau syndrome
- Sturge-Weber syndrome
- PHACES syndrome
- Ataxia telangiectasia
- Epidermal nevus syndrome
- Incontinentia pigmenti

NEUROFIBROMATOSIS

The neurofibromatosis (NF) encompasses three distinct inherited disorders that share the propensity to develop multiple benign tumors of the peripheral and/or central nervous system. These include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 and schwannomatosis. **Table 1** gives a brief overview of each of these conditions. Cutaneous lesions are described here.

Dermatological Features

Café au lait spots (Fig. 1)
- They are the first manifestation of NF1 to appear and they are frequently present at birth.
- Size/shape/contour is of no diagnostic significance and number of café au lait macules does not correlate with severity of NF.

Intertriginous Freckling (Fig. 2)
- Also called Crowe's sign. It is the most specific sign of NF1.
- Café au lait spots less than 5 mm are referred to as freckles are present in axillae, inguinal region, inframammary areas.

- Palmar freckling is seen in 90% of Indian neurofibromatosis patients and it is called as the Patrick Yesudian Sign **(Fig. 3)**

Discrete Neurofibromas (Fig. 4)
- Neurofibromas are benign tumors of the nerve sheath that can occur at any point along any peripheral nerve, from spinal root to the cutaneous free nerve endings.
- They can be focal (localized to a single site on the nerve) or plexiform. The neurofibromas that present as dermatological complaint include the cutaneous, subcutaneous and superficial plexiform variants.

Figure 1 Multiple café au lait macules in a patient with NF1

Figure 2 Axillary freckling (Crowe's sign)

Table 1 Classification of neurofibromatosis

	Neurofibromatosis 1	*Neurofibromatosis 2*	*Schwannomatosis*
Incidence	1 in 3000	1 in 25,000	1 in 50,000
Inheritance	Autosomal Dominant	Autosomal dominant	Autosomal dominant
Gene/Chromosome	NF1/17q11.1	NF2/22q12q12.2	INI1/SMARCB1/22q12.2
Protein	Neurofibromin	Merlin	Chromatin remodelling complex
Cutaneous features	Café au lait macules, axillary freckling, neurofibromas	Café au lait macules, no freckling, schwannomas	Painful subcutaneous or deep tissue nodules, no Café au lait macules or freckling

Figure 3 Palmar freckling (Patrick Yesudian sign)

Figure 4 Cutaneous neurofibromas

- Cutaneous neurofibromas are usually first noticed in adolescence and continue to increase in number and size throughout adulthood. Buttonholing sign is positive. The cutaneous neurofibromas are usually asymptomatic but cause cosmetic disfigurement. They can be pruritic and at times get infarcted to cause pain and swelling.
- Subcutaneous neurofibromas are less prevalent and arise along the peripheral nerve under the skin. They are well defined, ovoid, firm subcutaneous nodules, best appreciated with palpation. They can cause neurological symptoms such as paresthesia and weakness.
- Plexiform neurofibromas develop along the length of a nerve and involve multiple nerve fascicles and even multiple branches of a nerve giving a *bag of worms* sensation on palpation. They are usually present at birth or may develop years later. They can be associated with overlying hyperpigmentation, hypertrichosis and/or increased vascular markings and occasionally with overlying soft tissue overgrowth leading to massive hypertrophy and disfigurement **(Fig. 5)**.

Other Dermatological Associations
- Presence of Juvenile xanthogranuloma in cases of NF1 has a high predisposition to develop juvenile myelomonocytic leukemia, but this concept is still controversial
- Generalized hyperpigmentation
- Multiple glomus tumors.

Treatment of Cutaneous Lesions
- *Café au lait spots*: Q-switched ruby laser, continuous mode copper vapor laser and Erbium-YAG lasers can be used.
- *Cutaneous neurofibromas:* Removal of neurofibromas is indicated to improve cosmesis or to prevent local irritation or compression.
- Severe pruritus can be managed by antihistamines. If not controlled, ketotifen can be added. CO_2 laser excision of neurofibromas can be performed under general anesthesia which can decrease the disabling pruritus.
- *Plexiform neurofibromatosis:* Surgical debulking is done either to improve cosmesis or to prevent loss of function.

Chemotherapeutic trials have been done with pirfenidone (antifibrotic agent), and farnesyl transferase inhibitor, that down

Figure 5 Plexiform neurofibroma

regulates *RAS* oncogene. Newer agents tried include AZD2171 which is potent inhibitor of VEGF; sirolimus mammalian target of rapamycin (mTOR) inhibitor; PEG interferon α2b; and photodynamic therapy.

TUBEROUS SCLEROSIS

Tuberous sclerosis (TSC), also called as Bourneville disease, Pringle disease or Epiloia, is a condition inherited as an autosomal dominant trait but has a high spontaneous mutation rate. The condition is fully penetrant.

Two genes are responsible, *TSC1* on chromosome 9q34 which encodes for the protein hamartin and *TSC2* on chromosome 16 which encodes for the protein tuberin. These are tumor-suppressor genes, which when deficient result in mTOR disinhibition and abnormal proliferation of tissues, resulting in hamartomas. Cutaneous involvement of tuberous sclerosis along with the treatment is summarized in **Table 2**. Other dermatological features include fibromas around the teeth and even on the tongue; dental pits particularly affecting adult teeth; and skin tags called molluscum fibrosum pendulum, especially around the neck.

Table 2 Cutaneous lesions in tuberous sclerosis

Cutaneous lesion	Incidence, age of presentation, clinical presentation, histopathology, prognosis and treatment
Hypomelanotic macule (Fig. 6)	• 90% present at birth or appear within 1st few years of life. • 1–10 in number, 0.5–3 cm diameter of white macules. Some are oval at one end and taper to a point at the other. Hence, called lanceolate or ash leaf macules. Confetti pattern of small discrete hypomelanotic macules on arms and legs is not uncommon. • Normal number of melanocytes, but absent melanosomes. • Fade or disappear in adulthood. New lesions can appear as age increases. Treatment consists of camouflage.
Facial angiofibromas (Fig. 7)	• 75–90%. • Onset at 2–5 years. Occasionally can arise for the first time in adult life. • Heralded by excessive facial flushing in infancy. Later, 1–3 mm in diameter, pink to red papules that have a smooth surface. Occur on the central face often concentrated over the alar grooves extending symmetrically over the cheeks, nose, nasal opening and chin with relative sparing of the upper lip and lateral face. Lesion can occur on forehead, scalp or eyelids. • Epidermis shows extensive hyperkeratosis. Plump, spindle shape or stellate fibroblastic cells are seen in the dermis among increased number of dilated vessels. Collagen fibers are oriented in onion skin pattern around follicles and vessels. • During puberty they may grow in size and number. In adulthood they tend to be stable in size but redness may gradually diminish. Treatment options include electrodesiccation, cryosurgery, dermabrasion, excision, curettage, chemical peels and lasers. Topical rapamycin has been tried.
Fibrous facial plaque	• Incidence: 20–40 % of patients. • Congenital or appears shortly after birth. • Initially it looks like a capillary hemangioma, but when fully developed they are irregular soft to firm with color of normal surrounding skin, red or hyperpigmented in dark colored individuals. Plaques can also be found on scalp, cheeks and elsewhere on the face. • Connective tissue nevi of collagen type without vascular dilatation. • Does not spontaneously regress. Treatment consists of surgical excision, radiofrequency, curettage, and dermabrasion.
Shagreen patch (Fig. 8)	• Seen in 50% of the patient. • May present in infancy but can present later. • Initially look like capillary hemangioma but there is palpable thickening of the dermis. Later form a firm or rubbery irregular plaque ranging from 1 to 10 cm. Surface may appear bumpy with coalescing papules or nodules or the patch may have surface appearance of an orange peel. It is most commonly found on the back or buttocks and less commonly on the thighs. • Sclerotic bundles of collagen are found in the reticular dermis. Elastic fibers are typically reduced or absent. • Do not spontaneously regress. • Usually left untreated but may be excised.
Ungual fibromas/ Koenen's tumors	• Found in 88% adults. • Usually appear after the first decade. May sometimes first appear in middle age. • 1 mm to 1 cm in diameter. They arise from under the proximal nail fold or under the nail plate. They press on the nail matrix and cause a longitudinal groove and sometimes a groove forms without a papule. Subungual fibromas can be seen through the nail plate as red or white oval lesions or as red papules emerging from the distal nail plate causing distal subungual onycholysis. • Histology shows angiofibromas, but with more extensive hyperkeratosis and a variable increase in vascularity. • Do not spontaneously regress. • Usually treated by excision but have a high recurrence rate.

Figure 6 Ash leaf macule

Figure 7 Adenoma sebaceum (cutaneous angiofibromas)

Figure 8 Shagreen plaque

VON HIPPEL–LINDAU DISEASE

Von Hippel–Lindau disease, also referred to as central nervous system (CNS) angiomatosis, is inherited in an autosomal dominant fashion with incomplete penetrance. Both sexes are equally affected. Cutaneous findings include port-wine stains and café-au-lait macules. Other manifestations are vascular malformations in the cerebellum and brain stem. Retina is also commonly affected. There may be cystic neoplasms or angiomatous lesions in the kidneys, liver and pancreas.

STURGE-WEBER SYNDROME

Encephalotrigeminal Angiomatosis, Oculomeningeal Nevus Flammeus

Sturge-Weber syndrome is defined as facial port-wine stain in association with ipsilateral plial (i.e., leptomeningeal) vascular anomalies (with one or more symptoms; epilepsy early in life, hemiparesis or hemiplegia, gyriform intracranial calcifications, and cerebral atrophy) and inconstant ipsilateral choroidal vascular lesions with glaucoma. Port wine stain is present at birth as flat red patches involving at least the 1st branch (ophthalmic) with or without the involvement of the II or III branch. The lesions are usually unilateral, but can be bilateral and can even have skip areas.

MRI with contrast is the imaging modality of choice to detect leptomeningeal angiomas. Calcifications are best seen with CT scan of brain.

PHACES SYNDROME

The syndrome denotes *P*osterior fossa malformations, *H*emangiomas, *A*rterial abnormalities *C*oarctation of aorta and other *C*ardiac defects, *E*ye abnormalities, *S*ternal cleft and supraumbilical raphe syndrome. There is female preponderance and pathogenesis is unknown. Large facial hemangiomas may be associated with a Dandy-Walker malformation, vascular abnormalities. Other anomalies included hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum and septum pellucidum. Cerebrovascular anomalies can result in acquired, progressive vessel stenosis and acute ischemic stroke.

ATAXIA TELANGIECTASIA

Ataxia telangiectasia is an autosomal recessive disorder, a syndrome of progressive cerebellar ataxia beginning in early infancy, progressive oculocutaneous telangiectasia, a tendency to sinopulmonary infections, selective immunodeficiencies, and chromosomal instability with persistent DNA damage after irradiation. The initial manifestation is usually ataxia which typically becomes apparent when the child begins to walk. The oculocutaneous features are manifested by 3–6 years of age. The conjunctival telangiectasias are symmetric and involve the canthal areas involving the sclerae. Cutaneous telangiectasias appear in the butterfly distribution across the face, eyelids, ears, developing on the sun exposed areas. The progeric changes of the skin and hair are noted in almost 90% of patients. Myoclonic jerks, choreoathetosis oculomotor abnormalities, and dysarthric speech often become prominent in older children. Patients are usually confined to a wheelchair by the time they are 11 years old. Death frequently occurs in late childhood or early teenage years. Treatment of patients with ataxia telangiectasia is supportive.

EPIDERMAL NEVUS SYNDROME

Epidermal nevi are congenital hamartomas of embryonal ectodermal origin classified on the basis of their main component; the component may be sebaceous, apocrine, eccrine, follicular or keratinocytic. Epidermal nevus syndrome is a sporadic neurocutaneous linkage of congenital ectodermal defects in the skin, eyes, brain and skeleton. About 8% of the patients with epidermal nevi have systemic involvement, and 10–18% of the patients have systemic developmental disorders. Two-thirds of patients with epidermal nevus syndrome demonstrate associated neurologic findings, including cortical dysplasia, glial hamartomas, and low-grade gliomas. Cerebral and cranial anomalies, predominantly hemimegalencephaly and enlargement of the lateral ventricles, were reported in 72% of cases. Incidence of epilepsy has been reported as high as 75% and mental retardation as high as 60%. Focal neurologic signs including hemiparesis and homonymous hemianopia may also be seen.

INCONTINENTIA PIGMENTI

Bloch-Sulzberger Syndrome

It is an X-linked dominant disorder reported primarily in females. It is believed to be embryonic lethal in majority of males. It is caused by mutation in the gene NEMO [nuclear factor κβ (NF–κβ) essential modulator] on X chromosome xq28. In incontinentia pigmenti (IP) females, through the process of lyonization there is inactivation of one of the two X chromosomes. Staging is described in **Table 3**. Other clinical features and associations are listed in **Table 4**. In the vesicular stage it is important to guard against infection. Regular screening for retinal abnormalities is important especially at birth and in the first 3 months. Genetic counseling and examination of first degree relatives should be observed.

Table 3 Stages of incontinentia pigmenti

Stage	Age of onset	Etiopathogenesis, clinical features, and histopathology
Vesicular stage	From birth to shortly thereafter	• It is caused due to the population of the NEMO deficient cells that fail to activate NF-κβ leading to apoptosis. • Blisters preceded by erythema appear in crops with linear distribution along the limbs and circumferentially around the trunk. In general, vesicles clear within 1st few months of life, although they may recur during acute febrile illnesses in later life. • Massive infiltration of eosinophils and marked peripheral leukocytosis with up to 65% eosinophils is seen.
Verrucous stage (Figs 9 and 10)	2–8 weeks of life	• The number of the NEMO deficient cells decreases secondary to apoptosis and replaced by cells expressing normal allele. Hence, compensatory hyperkeratosis of the normal keratinocytes. • Lesions are predominantly seen over the distal limbs especially digits and ankles. They do not necessarily appear at the sites of vesicles. They usually clear by 3 years of age. • Hyperkeratosis, papillomatosis and mild dyskeratosis are seen.
Hyperpigmented stage (Fig. 9)	Several months of age to adulthood	• Incontinence of the melanin pigment from the destroyed epidermis into the dermis. • Hyperpigmented streaks and whorls along the lines of Blashcko are characteristic. Histology reveals melanin laden melanophages with extensive deposits of melanin in the basal layer and dermis. Vacuolization and degeneration of the epidermal basal layer is seen.
Hypopigmented stage	From infancy to adulthood	• Represents postinflammatory dermal scarring. Typical lesions consist of linear atrophic hairless scars following Blaschko's lines. They are less frequently observed on the trunk and seen more often on the posterior aspects of the upper and lower legs, and over shoulders and arms. • *Histology:* Normal number melanocytes or decrease in the number of melanocytes is seen. Epidermis is thinner and there is absence or reduction of the skin appendages which contributes to the impression of hypopigmentation.

Figure 9 Overlap of verrucous and pigmentary stages of incontinentia pigmenti

Figure 10 Verrucous stage of incontinentia pigmenti

Table 4 Clinical features and associations of incontinentia pigmenti

Nails	Hair	Teeth	Breast	Eyes	Brain
Ridging, pitting, and severe dystrophy	Alopecia, sparse hair in childhood and lustreless wiry coarse hair in adulthood	Hypodontia, delayed eruption, impaction, malformation of crowns and accessory cups	Unilateral breast and nipple aplasia, Supernumerary nipples	Strabismus, refractive errors, microophthalmos, cataracts, optic atrophy, and retinal ischemia leading to neovascularization	Seizures and mental retardation

MORE ON THIS TOPIC

Korf BR. Genodermatoses. In: Schachner LA, Hansen RC. Pediatric Dermatology. 4th ed. Mosby Elsevier; 2011. p. 128.1.

Thappa DM. Genodermatoses. In: Thappa DM. Clinical Pediatric Dermatology. 1st ed. Noida: Elsevier; 2009. p. 145.

Theos A, Boyd K, Korf B. The Neurofibromatoses. In: Harpers. Textbook of Pediatric Dermatology. 3rd ed. West Sussex: Blackwell Publishing Ltd; 2011.p.128.1.

Chapter 48.13
Vesiculobullous Disorders
Bhawna Wadhwa, Rashmi Sarkar

A wide array of vesiculobullous lesions can occur in the neonates, infants and in older children. Most of these entities have their etiopathogenesis, clinical features and management similar to that in adults. Although most of them are benign and transient, some may be serious and life-threatening and frequently cause parental anguish. So they should be recognized and treated promptly. The differential diagnosis of pediatric vesiculobullous lesions is summarized in **Box 1**. Disorders of the newborn and those associated with infection have been discussed earlier. A few common noninfective vesiculobullous conditions that are encountered in routine outpatient and emergency set ups will be discussed in this chapter.

IMMUNOBULLOUS DISORDERS

Immunobullous diseases in childhood are uncommon, but should be considered, if the blistering condition has been persistent for longer than a month, particularly, if unresponsive to antibiotic therapy.

Pemphigus

Neonatal pemphigus displays clinical, histologic and immuno-pathologic signs of pemphigus vulgaris (PV). It occurs when maternal IgG crosses the placenta, causing disease in the neonate. It may be mild or severe enough to cause stillbirth. It generally remits when maternal antibodies decrease (~6–12 months). In a study from North India, children less than 15 years accounted for 3.7% cases of pemphigus.

BOX 1 Differential diagnosis of pediatric vesiculobullous lesions
Transient disorders
Erythema toxicum neonatorum; neonatal pustular melanosis; miliaria crystallina and rubra; neonatal acne (benign cephalic pustulosis); and sucking blisters
Infections
Staphylococcal skin infections: bullous impetigo, staphylococcal scalded skin syndrome; congenital and neonatal candidiasis; herpes simplex infection; neonatal varicella; scabies; congenital syphilis; malassezia pustulosis; *Listeria monocytogenes* infection; *H. influenzae* infection; Group A and B streptococcal infection; *Pseudomonas* infection; and cytomegalovirus infection
Immunobullous disorders
Pemphigus vulgaris; pemphigus foliaceus; chronic bullous dermatosis of childhood (linear IgA disease); bullous pemphigoid; and dermatitis herpetiformis
Mechanobullous disorders
Epidermolysis bullosa
Miscellaneous conditions
Acropustulosis of infancy; incontinentia pigmenti; eosinophilic pustular folliculitis; erosive pustular dermatosis of the scalp; Langerhans' cell histiocytosis; hyperimmunoglobulin E syndrome; pustular eruption in Down syndrome; pustular psoriasis; neonatal Behçet disease; bullous mastocytosis; toxic epidermal necrolysis; epidermolytic hyperkeratosis; acrodermatitis enteropathica; and neonatal pustulosis of transient myeloproliferative disorder.

Pemphigus vulgaris (PV) It is rare in childhood. Painful flaccid blisters occur anywhere on the body, on normal or erythematous skin and rupture to form painful peripherally spreading erosions with no tendency to heal. Oral mucosal involvement occurs prior to skin involvement in majority of patients.

Pemphigus foliaceus (PF) It is more common in children than PV. It is characterized by small superficial flaccid bullae on normal or erythematous skin, that readily rupture to form crusted erosions, involving initially the seborrheic areas (face, scalp and upper trunk) but later becoming generalized. Mucosal involvement is rare.

Fogo selvagem (endemic pemphigus foliaceus) It occurs in densely forested areas of rural Brazil and affects children less than 14 years in 25% of cases.

Pemphigus herpetiformis It can rarely affect children. The earliest age of onset reported is 5 years.

Paraneoplastic pemphigus It is very rare in childhood and is associated with lymphoid neoplasms. The patients present with severe oral and conjunctival erosions with erythematous blistering. Polymorphic lesions with blisters and erosions that may resemble erythema multiforme are seen.

The diagnosis is established by Tzanck preparation to demonstrate acantholytic cells, skin biopsy to show the level of split, direct immunofluorescence that shows deposition of IgG in the intercellular substance and indirect immunofluorescence to demonstrate circulating IgG antibodies directed against cell surface of keratinocytes. The disease course and treatment modalities are essentially the same as in adults. Although corticosteroids (prednisolone 1–2 mg/kg) are the mainstay of treatment, adjuvant immunosuppressive drugs (cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, or methotrexate) may be needed in resistant cases. Intravenous immunoglobulins (IVIG) may be a promising therapy.

Bullous Pemphigoid (BP)

It is a subepidermal blistering disorder, rarely seen in children. Juvenile BP was first described by Lever in 1953. The onset is mostly before the age of 8 years. Early lesions may be pruritic urticarial or eczematous. Blisters are large, tense, hemorrhagic or filled with fibrinous fluid, arising on normal or erythematous skin on lower abdomen, inner thighs, flexor forearms or sometimes generalized (erythrodermic BP). Vesicles may develop on palms and soles especially in children. Mucous membrane involvement occurs in 10–35% patients. The erosions tend to re-epithelialize quickly and heal with hyperpigmentation.

The diagnosis is established by skin biopsy, direct immuno-fluorescence and indirect immunofluorescence. Treatment is with steroids or other immunosuppressives in recalcitrant cases. Localized BP can be treated with high-potency topical steroids. Some patients respond to sulfones, tetracycline, or nicotinamide.

Dermatitis Herpetiformis

It was described in infancy in 1956 by Leider. Majority of reported cases are more than 5 years of age. It is characterized by chronic, intensely pruritic, small papules and vesicles located symmetrically over extensor surfaces (elbows, knees, upper spine), scalp hairline and posterior nuchal area. Mucous membrane involvement is uncommon. Most of the cases have gastrointestinal abnormality similar to celiac disease but are asymptomatic. Anti-reticulin antibodies, and autoantibodies to endomysium (EMA), tissue transglutaminase (tTG) and gliadin may be detected.

Dapsone 2 mg/kg/day is the mainstay of treatment. Dietary management with a gluten-free diet may be effective. The disease is generally life-long, with relapses and remissions.

Chronic Bullous Disease of Childhood (CBDC)

It is a subepidermal blistering disorder of preschool children. Lesions are large tense bullae or vesicles, usually pruritic, on an erythematous base on the lower abdomen, perineum, lower extremities, and perioral area, but can be generalized with annular or polycyclic lesions **(Fig. 1)**. A characteristic feature is that new blisters appear at the periphery of the crusts of older bullae giving a *cluster of jewels* or *string of pearls* appearance. Mucous membranes are involved in up to 70% of cases. Bullous impetigo is an important differential diagnosis **(Fig. 2)**. Diagnosis is established by skin biopsy (subepidermal bulla with neutrophils along the BMZ), direct immunofluorescence (IgA in a homogeneous linear pattern along BMZ), and indirect immunofluorescence (low titer IgA serum autoantibodies).

Dapsone 2 mg/kg/day results in excellent disease control. Prednisone 1–2 mg/kg/day may be added in those who do not respond. Dicloxacillin, colchicine and sulfapyridine may be beneficial. The disease usually lasts several years and then remits. Occasionally, it may persist into puberty but with a lesser severity.

EPIDERMOLYSIS BULLOSA (EB)

This includes a group of rare genetic disorders with formation of blisters following minor physical injury. Nonscarring types demonstrate an intraepidermal separation (EB simplex) or a separation at the dermal–epidermal junction (junctional EB). In scarring types, subepidermal blisters are found (dystrophic EB).

Epidermolysis Bullosa Simplex

The most common form of EB simplex is Weber–Cockayne type and is usually diagnosed in early infancy, although it may not become evident until childhood. It primarily involves palms and soles, is aggravated by warm weather and hyperhidrosis is common. It improves with age.

Generalized EB simplex or Koebner type presents with generalized blistering within first year of life. Blisters are more common on distal extremities, especially the feet, knees, elbows and hands. In EB simplex, milia and scarring are usually absent, although some nail dystrophy may be seen.

EB herpetiformis (Dowling-Meara type) is the generalized form with pronounced oral mucosa involvement and grouped blisters.

Junctional Epidermolysis Bullosa

Two major forms of junctional EB exist. *Herlitz type* is the severe generalized form usually fatal before the age of 5 years. Blisters appear in the neonatal period. The pathognomonic feature is the development of exuberant nonhealing granulation tissue in periorificial skin, neck, ears, upper trunk and nail beds. Oral involvement, enamel dysplasia, extensive caries, frequent bacterial infections, dystrophic nails, growth retardation, ectropion, and scarring alopecia may be present. *Non-Herlitz* or *mitis variant* shows absence of granulation tissue and lack of involvement of most extracutaneous organs. There are mild but chronic ulcerations with poor healing, which may improve with age.

Dystrophic Epidermolysis Bullosa

Onset is usually at birth. Blisters, erosions, crusting, atrophic scarring, milia, and nail dystrophy are common features. It is slowly progressive and cutaneous squamous cell carcinoma may develop in both dominant and recessive forms. Severe recessive dystrophic EB of Hallopeau-Siemens is associated with extensive disease activity involving multiple organ systems including skin, eyes, oral mucosa, teeth, gastrointestinal tract, genitourinary tract and musculoskeletal system. Mitten glove deformity of hands and feet **(Fig. 3)**, knee contractures, anemia and growth retardation may be seen. The dominant dystrophic EB of Cockayne-Touraine type may have less severe blistering usually acral and lacks significant extracutaneous disease.

Diagnosis is established by clinical symptoms and skin biopsy. Electron microscopy is the gold standard. Immunofluorescence (antigenic) mapping and transmission electron microscopy helps to distinguish the different types of EB. Treatment is supportive with avoidance of trauma, wound management, temperature maintenance and nutritional support. Topical antibiotics, gauze wrapping, physical therapy (to prevent contractures), may aid in healing and reduce pain. Phenytoin, retinoids and vitamin E have been tried. Genetic counseling is an essential part of the management.

INFANTILE ACROPUSTULOSIS

An uncommon condition with recurrent crops of intensely itchy vesicopustules on the soles, sides of the feet and palms, but may also occur on the dorsa of the feet, hands, fingers, ankles, wrists and forearms, usually in the first year of life. Each crop

Figure 1 A 5-year-old child with chronic bullous disease of childhood

Figure 2 Bullous impetigo

Figure 3 Mitten glove deformity of hands in a patient of severe dystrophic epidermolysis bullosa

lasts for 7–14 days, tends to recur at intervals of 2–4 weeks. The severity of attacks gradually diminishes until they cease, usually within 2 years of the onset. Treatment includes potent topical corticosteroids, oral antihistamines and dapsone.

MORE ON THIS TOPIC

Duarte IB, Bastazini I Jr, Barreto JA, et al. Pemphigus herpetiformis in childhood. Paediatr Dermatol. 2010;27:488-91.

Fariba G, Ayotollahi A, Hejazi S. Pemphigus foliaceous. Indian Pediatr. 2012;49:240-1.

Howard R, Freiden IJ. Vesicles, pustules, bullae, erosions and ulcerations. In: Eichenfield LF, Freiden IJ, Esterly NB. Neonatal Dermatology. Saunders Elsevier; 2008. pp. 131-58.

Kanwar AJ, Ajith AC, Narang T. Pemphigus in North India. J Cutan Med Surg. 2006;10:21-25.

Thappa DM, Jeevan Kumar B. Chronic bullous disease of childhood. Postgrad Med J. 2003;79:437.

Wojnarowska F, Venning VA. Immunobullous diseases. In: Burns T, Breathnach S, Cox N, Griffiths C Rook's. Textbook of Dermatology. Vol 1, 8th ed. Wiley Blackwell; 2010. pp. 40.1-40.58.

Chapter 48.14
Papulosquamous Diseases
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Papulosquamous disorders are characterized by scaly papules and plaques. They consist of a diverse group of inflammatory conditions of the skin characterized by an eruption that exhibit papule and squamous components. Papulosquamous disorders during childhood can present a vast array of clinical findings. In Latin, papula means pimple and squames means scales.

Many other dermatological conditions may also become papulosquamous at some time during their course. These conditions are classified under different groups, based on other important characteristics, such as dermatophytoses, treponemal infections, nutritional deficiencies, *photosensitivity* dermatoses, pigmented purpuras and drug eruptions.

The prevalence of papulosquamous disorders varies from 2.5% to 10% in various studies. The major entities are listed in **(Box 1)**.

PSORIASIS

Psoriasis is a common chronic, inflammatory skin condition, typically characterized by raised, well-defined, erythematous skin lesions of varying size that are surmounted by silvery-white scales.

Epidemiology
Childhood psoriasis is relatively common and presents with lifetime prevalence estimated commonly at 1–3% of the general population. The peak age of onset of childhood psoriasis is varied. Data suggest that in 37% of psoriasis patients the disease appears before the age of 20 years, in 27%, by the age of 15 years, in 10%, by

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BOX 1 Common papulosquamous disorders in children
Psoriasis
Parapsoriasis
• Large-plaque parapsoriasis
• Small-plaque parapsoriasis
• Pityriasis lichenoides
– Pityriasis lichenoides et varioliformis acuta (PLEVA)
– Pityriasis lichenoides chronica
Lichen planus
Lichen nitidus
Lichen striatus
Pityriasis rosea
Pityriasis rubra pilaris

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the age of 10 years, in 6.5%, the disease manifests before the age of 5 years and in 2%, by the age of 2 years.

Etiopathogenesis
Etiology of psoriasis is multifactorial with an interaction of both genetic and environmental factors. There is a complex interplay of the vasculature, immune system and epidermis. A strong association exists between psoriasis, particularly early-onset psoriasis, and HLA-B17, HLA-Cw6 and HLA-DR-7 alleles. The association is strongest for the HLA-Cw6 allele in most ethnic groups. A number of genetic loci have been identified by genome wide linkage scans, and two loci have been replicated, psoriasis susceptibility 1 (PSOR 1) on chromosome 6 within the major histocompatibility complex, and PSOR 2 on chromosome 17q. Trigger factors for psoriasis include infection, trauma and drugs like antimalarials, nonsteroidal anti-inflammatory drugs and sudden withdrawal of systemic corticosteroids.

Clinical Features
Classic lesions are well-circumscribed erythematous plaques with overlying silvery scale.

The clinical variants of childhood psoriasis are enumerated with important features in **Table 1** and shown in **Figures 1 to 4**.

Differential Diagnosis
Napkin area psoriasis Seborrheic dermatitis, zinc deficiency, irritant contact dermatitis, intertrigo

Guttate psoriasis Pityriasis rosea, secondary syphilis, lichen planus, parapsoriasis

Plaque psoriasis Tinea, discoid lupus erythematosus, seborrhoeic dermatitis, psoriasiform dermatitis

Scalp psoriasis Tinea, seborrhoeic dermatitis

Pustular psoriasis Candidal miliaria, *eosinophilic* folliculitis, bacterial and viral folliculitis, acute generalized exanthematous pustulosis.

Treatment
Treatment goals are to improve the physical and psychological symptoms of psoriasis and minimize its adverse effects on future health and psychosocial development. *Topical treatment* is sufficient to control disease. Topical corticosteroids, calcipotriol and topical retinoid like tazarotene are used. Phototherapy, particularly narrowband UVB, has been proven as an effective therapeutic option for psoriasis in children with widespread plaque psoriasis resistant to conventional treatment. *Systemic therapy* is reserved for children with severe and otherwise

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Table 1 Clinical variants of childhood psoriasis

Plaque type	Most common type, plaques are often smaller and the scales are softer than adults. Facial lesions clearly demarcated than eczematous patches, are less itchy. Plaque lesions also involve scalp, palms and soles.
Guttate type	The lesions vary from 2–3 mm to 1 cm, round to oval appear over face, ears, scalp, trunk and extremities. Streptococcal infection triggers the guttate type of psoriasis.
Flexural type	Napkin area, axillae, genital and periumbilical area are involved.
Pustular type	Localized (palms and soles) and generalized forms are seen. Generalized type is subdivided into acute generalized pustular psoriasis of Von Zumbusch, annular/circinate type and pustular lesions localized to plaques of psoriasis.
Erythrodermic type	Rare in children, may start de novo or may develop in-patient with plaque type of psoriasis with exacerbation following irritant topical therapy or sudden withdrawal of systemic therapy.
Psoriatic diaper rash	Psoriatic diaper rash is bright red, well-demarcated often more shiny than seborrheic dermatitis and lacks the greasy yellowish scale.
Nail involvement	Nail changes are seen in long-standing cases. Pitting is the most common feature.
Psoriatic arthritis	Joint involvement is uncommon in childhood psoriasis.

Figure 1 Multiple erythematous guttate lesions on the extremities

Figure 2 Infant showing well defined brightly erythematous scaly plaque in the napkin area (Napkin psoriasis)

Figure 3 Erythematous scaly plaques of chronic plaque psoriasis

Figure 4 An 18-month-old boy showing erythematous plaques with pustules on the lesions and a few areas showing an annular pattern (pustular psoriasis)

treatment-refractory psoriasis. Methotrexate, retinoids, dapsone, hydroxyurea, cyclosporine and etanercept have all been used. The various indications and side effects of each modality of therapy has been highlighted in **Tables 2 and 3**.

PARAPSORIASIS

Parapsoriasis is a group of cutaneous T-cell lymphoproliferative disorder with close relationship with malignant lymphoproliferative disease. Clinically it is characterized by persistent, scaly and inflammatory skin lesions.

Epidemiology

Parapsoriasis is mainly a disease of adults. It has been described rarely in childhood and a few reports mention this condition as preceding early mycosis fungoides. In a study, 5% of small plaque parapsoriasis (SPP) and 20% of large plaque parapsoriasis (LPP) cases were children; males are more commonly affected than females.

Etiopathogenesis

Parapsoriasis is a cutaneous T-cell lymphoproliferative disorder with 1–10% of dominant T-cell clones. SPP, LPP and pityriasis lichenoides have all been shown to be monoclonal T-cell disorders. A *dominant* clone of lymphocytes has been demonstrated in a few cases of SPP. As this T cell clone did not undergo further mutations that are necessary for the development of mycosis fungoides, SPP is now thought to be a benign disorder with little or no potential to evolve into mycosis fungoides.

In LPP, the dominant clonal density has been 1–10% (in mycosis fungoides 50%). It is considered to be a premalignant condition because 10–30% of cases progress to overt mycosis fungoides. The risk is particularly high for patients with the retiform pattern of the disease.

Clinical Features

Small plaque parapsoriasis is characterized by asymptomatic, well-defined, skin colored papules and plaques with fine surface scale that imparts a wrinkled appearance. The lesions measure 3–6 cm in diameter and are usually localized to the trunk and proximal extremities. A digitate pattern resembling fingerprint marks on the sides of the trunk is particularly characteristic of SPP.

Large plaque parapsoriasis manifests as asymptomatic or mildly pruritic, irregular or oval, well demarcated or ill-defined patches or thin plaques, measuring more than 5 cm, localized

Table 2 Topical therapeutic agents used in the treatment of childhood psoriasis

	Indications	Side effects	Comments
Topical steroids	Psoriasis involving palms, soles, scalp and flexures	Atrophy, telangiectasia, striae	Potency should be chosen according to the site involved and age of the patient
Tar	Thick plaques	Irritation, staining, folliculitis	Messy procedure, obsolete these days
Anthralin	Thick plaques	Irritation, staining	Short contact therapy (30 min)
Calcipotriol	Palmoplantar involvement and thick plaques	Irritation	Recommended dose – 50 g/week/m^2
Tazarotene	Plaques	Irritation	–

Table 3 Systemic agents used in the treatment of childhood psoriasis

	Indications	Side effects	Comments
Methotrexate	Psoriasis vulgaris more than 10%, erythrodermic psoriasis, pustular psoriasis, psoriatic arthritis	Bone marrow suppression, hepatotoxicity	0.4–0.6 mg/kg/week
Cyclosporine	As Methotrexate	Renal toxicity, hypertension, electrolyte imbalance, hypertrichosis	3–5 mg/kg/day
Azathioprine	As Methotrexate	Comparatively safe	
Acitretin	Pustular psoriasis	Hepatotoxicity, dryness of skin, cheilitis, hyperlipidemia	0.5–1 mg/kg/day

to buttocks, lower trunk, upper thighs, inner upper arms and inframammary areas. The patches or plaques are reddish-brown or salmon pink in color. The surface is slightly scaly and with time develops a wrinkled, atrophic appearance. Atrophic changes are usually accompanied by telangiectasia and mottled pigmentation that is collectively known as poikiloderma. Hypopigmented patches are common in the Indian subcontinent **(Fig. 5)**. A rare variant is retiform parapsoriasis, which refers to a net-like or zebra-like pattern of scaly macules and papules that eventually becomes poikilodermatous in appearance.

Differential Diagnosis

Small plaque parapsoriasis should be differentiated from nummular eczema, plaque or guttate psoriasis, pityriasis rosea, tinea corporis, mycosis fungoides, and pityriasis lichenoides chronica.

Large plaque parapsoriasis should be differentiated from poikilodermatous skin conditions such as Rothmund-Thomson syndrome, Bloom's syndrome, dyskeratosis congenita, systemic lupus erythematosus, dermatomyositis, radiodermatitis, and mycosis fungoides.

Figure 5 Hypopigmented variant of parapsoriasis

Treatment

Small plaque parapsoriasis usually requires no treatment. Emollients, topical corticosteroids and UVB therapy may be used in symptomatic patients. LPP can be treated with emollients, topical potent corticosteroids, UVB and psoralen with UVA (PUVA) therapy. In case of malignant transformation, local radiotherapy is useful. PUVA therapy is an effective first-line therapy in treating parapsoriasis.

Prognosis

The SPP is clinically benign with no risk of progression to lymphoma. In contrast, the large plaque variety will progress to overt mycosis fungoides in 10–30% of cases.

PITYRIASIS LICHENOIDES

Pityriasis lichenoides is a benign lymphoproliferative disorder grouped under parapsoriasis. The types of which are pityriasis lichenoides chronica (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA) or Mucha-Habermann disease.

Epidemiology

Pityriasis lichenoides is a disorder of young adults and children. Pediatric age group constitutes 19–38% of the cases of pityriasis lichenoides with variable male predominance.

Etiopathogenesis

The presence of clonal T lymphocytes and occasional progression of PLC to mycosis fungoides suggests that it is a cutaneous lymphoproliferative disorder. Benign nature is due to vigorous host immune response mediated by CD8+ suppressor T lymphocytes.

Clinical Features

The eruption of pityriasis lichenoides can be found on any part of the body. It is usually symmetrically distributed on the trunk with varying degrees of involvement of the face, neck, and limbs. PLEVA usually begin with the sudden onset of 2–4 mm diameter red macules and papules, which evolve over several days into vesicular or hemorrhagic, necrotic, crusted and eroded lesions **(Fig. 6)**. The eruption appears in successive crops, which settle down over weeks to months.

Figure 6 Erythematous papulovesicular lesion on the trunk in PLEVA

Figure 7 Dull erythematous scaly papules and plaques on the trunk in pityriasis lichenoides chronica in a 2-year-old boy

Pityriasis lichenoides chronica can occur separately or in association with PLEVA. The characteristic lesion is a small, firm, lichenoid papule 3–10 mm in diameter, and reddish brown in color. An adherent *mica-like* scale can be detached by gentle scraping to reveal a shining brown surface, a distinctive diagnostic feature **(Fig. 7)**. Over the course of 3 or 4 weeks the papule flattens and the scale separates spontaneously to leave a pigmented macule, which gradually fades after sun exposure, which is the hallmark of the disease.

Differential Diagnosis

The acute form needs to be distinguished from varicella, insect bite reaction, *leukocytoclastic* vasculitis, septicemia, vesicular pityriasis rosea, and lymphomatoid papulosis. The chronic form mimics: pityriasis rosea, guttate psoriasis, secondary syphilis and lichen planus.

Treatment

No treatment is needed for mild cases that are asymptomatic. The treatment is aimed at controlling underlying infection and modulating the inflammatory response.

Topical treatments such as topical low or mid-strength corticosteroids and coal tar preparations are used. Phototherapy such as natural sunlight exposure or narrow-band ultraviolet B (NBUVB) can be used. PUVA is not recommended for children less than 11 years old.

Systemic therapies such as oral antihistamines, oral antibiotics: erythromycin (40 mg/kg/day in divided doses), tetracycline (1–2 g/day in divided doses), methotrexate (low dose) are used for severe ulcer necrotic form of the disease. Systemic corticosteroids and dapsone are also used in refractory cases.

LICHEN PLANUS

Lichen planus (LP) is a common inflammatory disorder characterized by violaceous, scaly, flat-topped, polygonal papules commonly involving the flexor aspects of the wrists, legs, oral and genital mucous membranes. The name is derived from the Greek word *leichen* meaning tree moss and the Latin word planus meaning flat. Erasmus Wilson first described it in 1869.

Epidemiology

In the international literature, the frequency of LP varied from 2.1% to 11.2% of the pediatric population. Childhood LP is more common in the tropics. Childhood LP consists 0.13% of total cases seen in pediatric dermatology. Although LP is usually sporadic, there is a familial form of LP. Familial LP is characterized by early age of onset, generalized involvement including oral mucosa and prolonged course with frequent relapses.

Etiopathogenesis

Its precise etiology is unknown. The occurrence of LP in monozygotic twins indicates a leaning toward genetic linkage. Recently, cell-mediated autoimmune response targeting basal keratinocytes has been suggested. The trigger for autoimmune response can be due to a virus or a drug or an allogeneic cell.

Clinical Features

Classical LP manifests as extremely pruritic, flat-topped, violaceous-colored, polygonal papules which measure 3–15 mm in diameter. Wickham's striae are evident on the surface of the papules as a reticulate network of fine linear white scales **(Fig. 8)**.

The distribution is bilaterally symmetrical. The common sites of involvement are wrists, lower back and pretibial areas, ankles, genitalia, sometimes can also involve face, scalp, and palmoplantar surfaces. The eruption in LP typically demonstrates the Koebner or

Figure 8 Violaceous papules with Wickham's striae on the forearm in lichen planus

isomorphic phenomenon, in which cutaneous lesions appear or extend in areas of trauma.

LP hypertrophicus and annular LP are more frequently seen in children. Eruptive LP where lesions appear in crops is common in tropical and subtropical countries.

The mucosal and nail involvement is less common in children. The less prevalence of oral LP in children has been attributed to less number of associated systemic disease, autoimmune disorders, infections and dental restoration procedures compared to adults.

Nail changes include longitudinal ridging, pitting, thinning of nail plate, trachyonychia, discoloration, nail dystrophy, subungual hyperkeratosis, onycholysis, nail splitting, thickening of nail plate and leukonychia in decreasing order of frequency.

Differential Diagnosis
The important differential diagnoses are lichenoid drug eruptions and graft-versus-host disease (GVHD). LP also needs to be differentiated from psoriasis and pityriasis rosea. Violaceous, flat topped papules with Wickham's striae, distribution of the lesions and mucosal involvement helps in distinguishing LP from other disorders.

Treatment
Topical corticosteroids are the mainstay of treatment for localized and classical LP. Topical steroids can be combined with oral corticosteroids (0.5–1 mg/kg/day) administered as a tapering dose over a 2–12 week period. Other therapies of childhood lichen planus include dapsone, oral acitretin, antimalarials, thalidomide, cyclosporine, azathioprine, and mycophenolate mofetil. Topical treatment options for oral LP include corticosteroids in orabase, topical tretinoin and isotretinoin gel. In nail LP, *tazarotene* gel is used topically on the periungual folds, if few nails are involved.

Prognosis
Children tend to have a more chronic and prolonged course. Response to treatment and prognosis of oral LP in children is favorable when compared to adults. Malignant transformation of mucosal and hypertrophic LP has not been reported in children. There may be an increased transformation into squamous cell carcinoma in children with familial LP.

LICHEN NITIDUS
It is a chronic, papulosquamous eruption characterized by multiple, 1–2 mm, flesh-colored, shiny, sharply demarcated, dome-shaped papules. It is a clinically and pathologically distinct inflammatory disorder commonly occurring in children.

Epidemiology
The disease is common in preschool, school-going children and young adults. The peak incidence in children is between 7 years and 13 years. It is more common in males.

Etiopathogenesis
The etiology is unknown. Familial cases of lichen nitidus (LN) have been reported. Cases of coexisting LP and LN have been reported and there are significantly fewer T-helper cells in LN than in LP. In some cases sun exposure may also play a role in the pathogenesis.

Clinical Features
The characteristic lesions are multiple, monomorphic, tiny, pinpoint to pinhead sized, flesh colored, shiny, flat or dome shaped papules, which characteristically exhibits the Koebner phenomenon **(Fig. 9)**. Occasionally, fine overlying scale or a hyperkeratotic plug may be seen. The sites involved are penis,
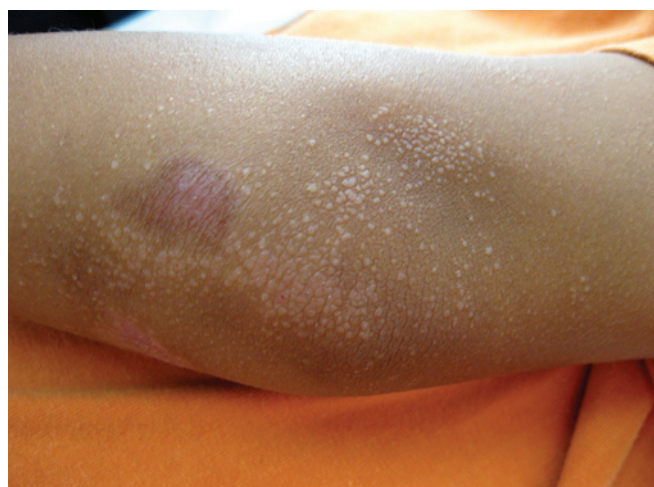
Figure 9 Multiple flat topped skin colored shiny papules on the elbows in lichen nitidus

genitalia, abdomen, and extremities or, less frequently, may occur as a generalized condition.

Differential Diagnosis
The important differential diagnoses are early lesions of LP, and frictional lichenoid eruptions. LN with lesions on photo-exposed areas has to be differentiated from polymorphous light eruptions. The characteristic histology confirms the diagnosis.

Treatment
No treatment is required in most cases. Symptomatic relief can be achieved with mid potency topical corticosteroids and oral antihistamines.

LICHEN STRIATUS
Lichen striatus is a benign, self-limiting, linear, inflammatory dermatosis of unknown etiology that usually affects children between 5 years and 15 years of age.

Etiopathogenesis
The etiology is unknown. Several theories have been proposed including environmental agents, cutaneous injury, viral infection, hypersensitivity and genetic predisposition. The development of lesions along the lines of Blaschko suggests that the cutaneous defect may result from a somatic mutation that arises embryologically.

Clinical Features
The lesions are characterized by small, pink, lichenoid papules, discrete at first but rapidly coalescing, appear suddenly and extend over the course of a week or more to form a dull-red, slightly scaly linear band, usually 2 mm to 2 cm in width, and often irregular, along the Blaschko's lines **(Figs 10 and 11)**. The lesions are usually localized to limbs but can involve trunk, neck, face and buttocks. The lesions may be multifocal involving more than one body part, unilateral or bilateral.

Treatment
Lichen striatus being a benign and self-limiting condition, treatment is usually unnecessary. Reassurance regarding the course and prognosis is required. Low-strength topical steroids or topical tacrolimus 0.03% at night for 1–2 months may be beneficial to hasten resolution.

Figure 10 Erythematous scaly papules, linear distributed over 2 dermatomal regions on the side of the trunk in lichen striatus

Figure 11 Linear hypopigmented papules on the extremities in lichen striatus

PITYRIASIS ROSEA

Pityriasis rosea (PR) is an acute, self-limiting papulosquamous disorder of unknown etiology characterized by scaly erythematous patch or plaque known as the herald patch, which heralds the onset of a widespread papulosquamous eruption in the classical *fir tree or Christmas tree* distribution.

Etiopathogenesis

Although the cause of PR has not been established, the frequent reporting of a viral-like prodrome, clustering of cases, occasional occurrence among close contacts and peak incidence in winter and early spring suggest a viral etiology. Human herpesvirus (HHV)-6 and HHV-7 have been suggested as a cause for the eruption. Other infective agents considered as causes are fungi, streptococci, *Legionella pneumoniae, Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, cytomegalovirus and Epstein-Barr virus.

Clinical Features

The primary eruption, herald patch (mother spot), usually situated on the thigh or upper arm, the trunk or the neck, is a sharply defined, erythematous, round or oval plaque, covered by fine collarette scale **(Fig. 12)**. The secondary eruption occurs after an interval of 5–15 days, but may be as short as a few hours or as long as 2 months. The general eruption begins to appear in crops at 2- to 3-day interval over a week or 10 days.

Differential Diagnosis

Diagnosing a case of PR is not difficult because of the characteristic collarette of scale and typical distribution, but few conditions should be ruled out. Herald patch should be differentiated from tinea and the following conditions can mimic the secondary eruption—guttate psoriasis, secondary syphilis, nummular eczema and parapsoriasis.

Treatment

Most children require no therapy. For all patients, education about the disease process and reassurance should be given. Topical steroids can be used for patients with associated pruritus. Oral antibiotic erythromycin and acyclovir have been tried to shorten the course of the disease mainly in adults.

Figure 12 Skin colored small plaques with a peripheral collarette of scales

Prognosis

It is self-limiting and resolves with or without therapy over 4–12 weeks. It may result in postinflammatory hypo- or hyperpigmentation.

PITYRIASIS RUBRA PILARIS

Pityriasis rubra pilaris (PRP) is a chronic papulosquamous disorder of unknown etiology characterized by palmoplantar keratoderma, follicular plugging and erythematous perifollicular papules that may progress to plaques or to erythroderma with distinct areas of uninvolved skin, the so-called islands of sparing. It is a chronic skin disorder with variable clinical spectrum.

Epidemiology

Pityriasis rubra pilaris has been reported around the world with the prevalence varying from 1 in 5,000 to 1 in 50,000 in various populations. A bimodal incidence of PRP in 1st and 5th decade has been demonstrated. The percentage of reported cases belonging to type III, type IV and type V in three reported series are 4–14%, 7–24%, and 4–14%, respectively. The type III and type IV usually manifest in the first decade of life. Type V is usually present at birth or develops in the first few years of life.

Figure 13 Grouped follicular papules on the shoulder and arms in pityriasis rubra pilaris (PRP)

Figure 14 Plantar keratoderma of both feet in pityriasis rubra pilaris (PRP)

Etiopathogenesis

Its etiology is unknown. Increased epidermal cell proliferation and reduced levels of retinol-binding protein that is a specific carrier of vitamin A are observed in PRP. An infective etiology is suggested in the form of bacterial superantigens especially in the juvenile form. Currently, a reactive hypersensitivity in response to infection resulting in T-cell mediated autoimmunity has been proposed.

Clinical Features

Pityriasis rubra pilaris is divided into six types. The Griffiths classification includes types I through VI, as follows:

- Type I is classic adult PRP. This is the most common form of PRP, accounting for more than 50% of all cases of PRP. Onset is acute, and the features are classic, including erythroderma with islands of sparing, palmoplantar keratoderma, and follicular hyperkeratosis **(Figs 13 and 14)**. This type of PRP has the best prognosis.
- Type II is atypical adult PRP. This form accounts for about 5% of all cases of PRP. It is characterized by ichthyosiform lesions, areas of eczematous change, alopecia, and a prolonged course.
- Type III is classic juvenile PRP. This form accounts for about 10% of all cases of PRP. It is very similar to type I; however, its onset is within the first 2 years of life. Remission can occur sooner than with type I, within an average of 1 year.
- Type IV is circumscribed juvenile PRP. This form accounts for about 25% of all cases of PRP. It occurs in prepubertal children and is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema of the knees and the elbows. The long-term outcome is unclear, with some reports of improvement in the late teens. This form of PRP rarely progresses.
- Type V is atypical juvenile PRP. This form accounts for about 5% of all cases of PRP. Most cases of familial PRP belong to this group. It has an early onset and runs a chronic course. It is characterized by prominent follicular hyperkeratosis, scleroderma like changes on the palms and the soles, and infrequent erythema.
- Type VI is HIV-associated PRP. Patients with HIV may have nodulocystic and pustular acneiform lesions. Elongated follicular plugs or lichen spinulosus–type lesions have also been reported to be present. Patients' conditions tend to be resistant to standard treatments, but they may respond to antiretroviral therapies.

Differential Diagnosis

Pityriasis rubra pilaris should be differentiated from psoriasis, atopic dermatitis, lichen planus, lichen nitidus, viral exanthem, Kawasaki disease and nonbullous congenital ichthyosiform erythroderma.

Treatment

Topical treatments include the use of emollients, keratolytics like 2–5% salicylic acid, topical corticosteroids, retinoic acid 0.05%, hydrating agents and calcipotriene. Among systemic therapies, acitretin is the drug of choice with a dose of 0.5–0.75 mg/kg/day. Regular monitoring of fasting blood lipids and liver function tests are important. Methotrexate and cyclosporine have also been tried.

MORE ON THIS TOPIC

Capella GL, Finzi AF. Psoriasis and other papulosquamous diseases in infants and children. Clin Dermatol. 2000;18:701-9.

Chuh A, Lee A, Zawar V, et al. Pityriasis rosea—an update. Indian J Dermatol Venereol Leprol. 2005;71:311-5.

Cohen BA. Papulosquamous eruptions. In: Cohen BA. Pediatric Dermatology. 3rd ed. Philadelphia: Elsevier; 2005. pp. 67-99.

Dogra S, Kumar B. Epidemiology of skin diseases in school children: a study from Northern India. Pediatr Dermatol. 2003;20:470-3.

Fox BJ, Odom RB. Papulosquamous diseases: a review. J Am Acad Dermatol. 1985;12:597-624.

Hogan PA. Papulosquamous disease. In: Schachner LA, Hansen RC, eds. Pediatric Dermatology. 3rd ed. Philadelphia: Elsevier Publishers; 2003. pp. 643-81.

Lokre S, Hiremagalore R. Childhood psoriasis—Clinical manifestations. Indian J Paeditr Dermatol. 2012;13:3-8.

Ragunatha S. Lichen planus, lichenoid disorders and other papulosquamous disorders. In: Inamadar AC, Palit A, Ragunatha S, eds. Textbook of Pediatric Dermatology, 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2014. pp. 381-96.

Chapter 48.15

Ichthyosis

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Ichthyosis is a clinically and genetically heterogeneous group of disorders of keratinization, characterized by a diffuse, generally uniform and persistent pattern of scaling without significant mucosal or extracutaneous involvement. Ichthyosiform syndromes present with extracutaneous involvement apart from the scaling.

Ichthyosis can be inherited or acquired. *Acquired ichthyosis* is a noninherited ichthyosis associated with nutritional, metabolic, infectious, endocrinological, malignant, inflammatory **(Fig. 1)** and neurologic diseases or medications. As pediatricians are likely to deal with inherited ichthyosis, the chapter focuses mainly on these. *Inherited ichthyoses* are a heterogeneous group of disorders with a worldwide distribution. For uniformity and ease of communication across the world an Ichthyosis Consensus Conference on the terminology and classification of inherited ichthyoses was held in 2009, the results of which are summarized in **Flow chart 1** and **Table 1**. For easier comprehension, it is essential to be familiar with some names and terms used in this context that are elaborated in **Table 2**.

COMMON ICHTHYOSIS

Ichthyosis Vulgaris

Ichthyosis vulgaris (IV; OMIM_146700) is the most common of the inherited ichthyoses and is often missed in clinical practice due to the often subtle clinical manifestation.

Prevalence 1:250–1:1,000; equal sex predilection.

Etiopathogenesis There is loss of function mutation in filaggrin gene [located within the epidermal differentiation complex (EDC) genes on chromosome 1q21], which is inherited as an autosomal dominant trait. Filaggrin (from *fil*ament *agg*regating prote*in*) is integral to late epidermal maturation as it binds to keratin filaments and causes flattening of stratum corneum, which acts as the epidermal barrier.

Clinical features Ichthyosis vulgaris usually manifests after 2 months of age with flaky or branny semi-adherent white or gray scales with characteristically up-turned edges. There is a generalized involvement with relative sparing of flexures and erythema, pruritus or eczema may be present. A strong association with atopy has been described. It is often confused with X-linked recessive ichthyosis (XLRI); further details which can distinguish these two entities are tabulated in **Table 3**. Differential diagnosis is listed in **Box 1**.

Prognosis Overall the condition is mild, may remain undiagnosed and improves with age. No systemic complications or internal organ involvement is seen.

X-Linked Recessive Ichthyosis

Prevalence It varies in different ethnic groups ranging from 1:2,000 to 1:6,000. Being X-linked recessive disorder, girls are not affected, but they act as carriers and may have subtle clinical features which can hint towards the diagnosis. It has a worldwide distribution.

Figure 1 Semi-adherent white or gray scales localized to erythematous plaques in a child with leprosy

Flow chart 1 Classification of ichthyosis
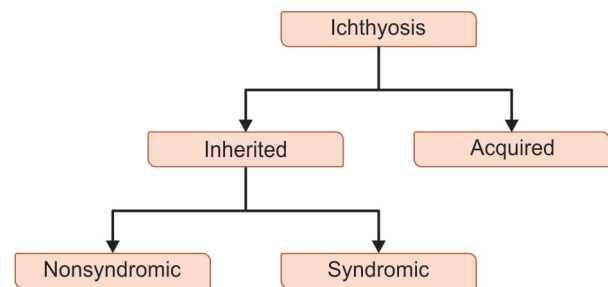
Table 1 Classification of inherited ichthyoses (Ichthyosis Consensus Conference, 2009)

Nonsyndrome ichthyoses	
Common:	Ichthyosis vulgaris, X-linked recessive ichthyosis
ARCI:	Autosomal recessive congenital ichthyosis, Harlequin ichthyosis, lamellar ichthyosis, congenital ichthyosiform erythroderma
Keratinopathic:	Epidermolytic ichthyosis, superficial epidermolytic ichthyosis
Others:	Loricrin keratoderma, erythrokeratodermia variabilis, peeling skin disease, Congenital reticular ichthyosiform erythroderma, keratosis linearis ichthyosis congenital keratoderma (KLICK)

Syndromic ichthyoses

X-linked ichthyoses: X-linked recessive ichthyosis, ichthyosis follicularis atrichia photophobia, Conradi-Hünermann-Happle syndrome

Autosomal ichthyoses

- *Prominent hair involvement*: Netherton syndrome, ichthyosis hypotrichosis syndrome, ichthyosis hypotrichosis sclerosing cholangitis, trichothiodystrophy
- *Prominent neurological involvement*: Sjögren-Larsson syndrome, Refsum syndrome, mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratodermia (MEDNIK)
- *Fatal disease*: Gaucher's, multiple sulfatase deficiency, cerebral-dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma (CEDNIK), arthrogryposis, renal dysfunction-cholestasis
- *Others*: Keratitis ichthyosis deafness (KID) syndrome, neutral lipid storage disorder, ichthyosis prematurity syndrome

Table 2 Common terms and names used with respect to ichthyosis

Disorder of keratinization/ cornification	A broadspectrum of skin disorders where there is abnormal differentiation of the epidermis and/or appendages, often with aberrant formation of the cornified envelope
Cornified envelope	Several layers of terminally differentiated, dead keratinocytes which forms the endpoint of epidermal differentiation and death and function as a barrier against the environment
Scaling	Visible flakes of stratum corneum
Hyperkeratosis	Histopathological increase in thickness of stratum corneum
Keratoderma	Localized form of hyperkeratosis
Ichthyosis (Gk *ichthys/ikhthus*, FISH -osis)	A clinically and genetically heterogeneous group of skin disorders, characterized by a diffuse and persistent pattern of scaling without mucosal or extracutaneous (except in ichthyosiform syndromes) involvement
Ichthyosiform syndromes	Ichthyosis with extracutaneous involvement
Retention ichthyosis	Ichthyosis resulting from defective desquamation of corneocytes, e.g., lamellar ichthyosis
Hyperproliferation ichthyosis	Ichthyosis resulting from increased proliferation of keratinocytes, these are usually associated with prominent inflammatory component, e.g., nonbullous ichthyosiform erythroderma
Inherited ichthyosis	Ichthyosis caused by genetic mutations which are inheritable
Acquired ichthyosis	Noninherited ichthyosis associated with nutritional, metabolic, infectious, malignancy, inflammatory and neurologic diseases or medications
Hystrix	Massive hyperkeratosis, cobblestone-like or spiky
Collodion	A syrupy solution of pyroxylin (nitrocellulose) in ether and alcohol which has medicinal and commercial uses
Collodion membrane	A generalized glistening, taut, yellowish film stretched over the skin. It resembles a clingfilm wrap. It cracks after some time and is shed.

Table 3 Comparison of ichthyosis vulgaris and X-linked recessive ichthyosis

	Ichthyosis vulgaris	*X-linked recessive ichthyosis*
Prevalence	1:250–1,000	1:2,000–6,000
Inheritance	Autosomal dominant with variable penetrance	X-linked recessive
Etiology	Filaggrin gene mutation	Steroid sulfatase (STS) gene mutation
Onset	Usually after 2–6 months	75% cases present within 1st week of life
Collodion membrane	Absent at birth	Mild collodion like changes may be present
Cutaneous presentation	Xerosis, scaling, pruritus, eczema	Scaling mainly, pruritus is unusual
Scaling type	Small, flaky or branny, and semi-adherent with turned-up edges	Medium to large, polygonal, adherent
Scaling color	White-gray	Dark brown or light gray depending on skin color
Distribution	Generalized distribution; extensors > flexures. Trunk—mildly affected; diaper area is spared. Facial scaling, generally on forehead and perioral, may be seen.	Generalized distribution; extensors > flexures; trunk—involved; posterior and lateral neck and preauricular facial skin are commonly affected.
Palmoplantar	Hyperlinearity present	spared
Erythema	Absent	Absent
Seasonal variation	Improves in summers	Improves in summers
Keratosis pilaris	Commonly present	Unusual
Course	Gradual improvement in adolescence	Increases throughout childhood, stabilizes in the teens
Hypohidrosis	Possible	Possible
Extracutaneous involvement	Strong association with atopy	Cryptorchidism/testicular maldescent, Inguinal hernia and unilateral renal agenesis. Corneal dot, thread-like or comma-shaped opacities
Carrier	—	Corneal dot, thread-like or comma-shaped opacities in female carriers (in ~ 24%)
Perinatal	—	Prolonged labor—one-third cases
Histopathology (Light microscopy)	Mild hyperkeratosis, diminished/absent granular layer. Features of keratosis pilaris may be seen.	Expanded stratum corneum without parakeratosis or acanthosis. Granular layer—usually normal
Ultrastructure	Scanty and fragmented keratohyaline granules in granular layer with normal keratin filaments.	Keratohyaline granules—normal/small and numerous; retained corneodesmosomes within stratum corneum
Special analyses	Reduced or absent stratum granulosum; negative filaggrin staining by antigen mapping	Absent steroid sulfatase activity (leukocytes or fibroblasts), FISH test for STS deletion; low maternal serum/urinary estriol levels (helps in *in utero* detection of XLRI).

Abbreviations: IV, ichthyosis vulgaris; FISH, fluorescent in situ hybridization; STS, steroid thiosulfatase; XLRI, X-linked recessive ichthyosis.

BOX 1 Differential diagnosis of ichthyosis vulgaris
• Atopic xerosis • X-linked recessive ichthyosis • Irritant dermatitis • Eczéma craquelé • Acquired ichthyosis • Refsum's disease.

Etiopathogenesis A mutation in steroid sulfatase (*STS*) gene located at the distal end of short arm of X-chromosome has been recognized. *STS* gene codes for the enzyme steroid sulfatase that is essential for gradual reduction in cholesterol sulfate levels in stratum corneum which triggers intercellular lipid bilayer disintegration and desquamation. The sulfated forms of some steroid sex hormones, such as 17-hydroxyprogesterone, estrone and dehydroepiandosterone, are also increased in patients with XLRI (OMIM_308100). The altered sex hormone profile may also explain the abnormal testicular development in some patients. Serum cholesterol levels are unaltered as they are synthesized by hydroxymethylglutamyl-CoA reductase.

Clinical features Mild collodion membrane may be noticed at birth, subsequently the child develops dark brown or gray colored medium to large sized polygonal plate such as scales prominently on the extensors with a tendency of encroaching on the flexures **(Fig. 2)**. Eczema or pruritus is unusual. Subtle points of difference from IV have been highlighted in **Table 3**.

Extracutaneous manifestations In a child with suspected XLRI, it is of utmost importance to look for evidence of cryptorchidism/ testicular maldescent. Inguinal hernia and unilateral renal agenesis is also more common in these patients. Ocular evaluation with the help of slit-lamp examination can reveal corneal dot, thread-like or comma-shaped opacities in 24–100% patients.

Perinatal manifestations Prolonged labor and the related complications may arise in nearly one-third of the babies due to placental steroid sulfatase deficiency leading to low maternal urinary estriol.

Prognosis Skin condition tends to worsen with age and then stabilizes by adolescence but it is generally a benign disorder apart from its extracutaneous manifestations.
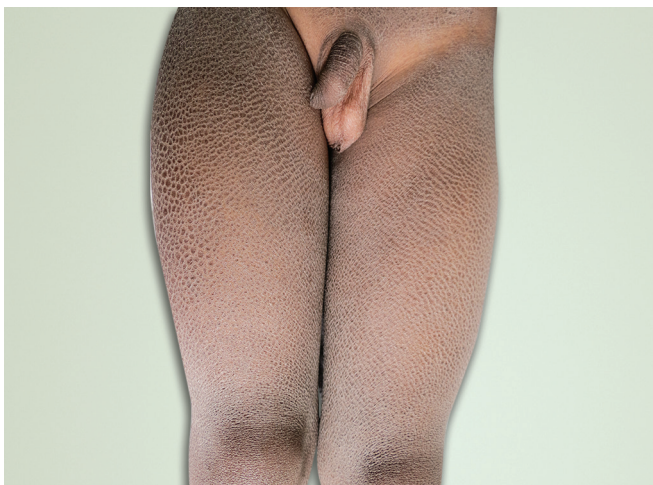
AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS

Lamellar Ichthyosis
The term *lamellar* is derived from the Latin word *lamella* which means plate. It is so called because of the characteristic plate like scales observed in the patient.

Prevalence Less than 1 in 300,000.

Etiopathogenesis The cornified envelope which acts as the major epidermal barrier arises from the intracellular protein precursors including loricrin and involucrin. These precursors are cross-linked to lipid ceramides in the granular layer by the action of transglutaminase 1 (*TGM1*). Mutation in *TGM1* (OMIM_ 242300) has been found to be the primary cause of lamellar ichthyosis (LI) and leads to defective cornification and retention ichthyosis.

Clinical features The presentation can be variable, from mild to very severe. Most of the affected infants present as collodion babies at birth and may have eclabium, ectropion and deformed aural/nasal cartilage. After shedding the membrane, the baby may show erythroderma but this is of less intensity than infants with nonbullous ichthyosiform erythroderma (NBIE)—an important and persistent distinguishing feature. Subsequently, large dark brown, plate-like scales develop usually in a generalized distribution **(Fig. 3)**. The other clinical features have been discussed in **Table 4**. Differential diagnosis is listed in **Box 2**.

Prognosis The condition tends to persist and worsen in winters. Prognosis is variable depending on the severity of the condition.

Harlequin Ichthyosis
Harlequin ichthyosis (HI) was one of the first genodermatoses to be recorded. It presents with a distinctive skin patterning and a very high mortality. It is a rare disorder.

Etiopathogenesis Lamellar bodies are source of golgi body derived polar lipids, lipid-processing enzymes, proteases and their inhibitors. ATP-binding cassette sub-family A member 12 (*ABCA12*) is an epidermal lipid transporter responsible for formation of these lamellar bodies. The lamellar body-derived intercellular lipid lamellae help in maintaining the epidermal

Figure 2 Dark brown colored, medium-sized polygonal scales prominently on the extensors. This child had normal scrotal contents

Figure 3 Lamellar ichthyosis with plate-like scales. Note persistent ectropion and eclabium

Table 4 Comparison of autosomal recessive congenital ichthyosis

	Harlequin ichthyosis	*Lamellar ichthyosis*	*Nonbullous ichthyosis erythoderma*
Inheritance	AR	AR	AR
Etiology	Missense mutations in *ABCA12*	Mutation in *TGM1* (transglutaminase)	Multiple mutations identified; *TGM1*, lipoxygenase 3 and 12; ichthyin; *ABCA12*
Onset	At birth, often preterm babies or stillborn	At birth	At birth
Collodion membrane	Severe	Present	Present
Cutaneous presentation	Encased in a rigid, taut, yellow-brown collodion membrane. Deep fissures, extreme ectropion, eclabium and contractures. Well-formed hands and feet encased in mitten-like casts	Collodion membrane with ectropion and eclabium; erythematous patches and deep, painful fissures. Hypoplasia of aural and nasal cartilages. Limitation of joint movement, flexion contractures	Collodion membrane or erythrodermic at birth. Followed by generalized scaly erythroderma. Ectropion, hypoplasia of the nasal/aural cartilages, nail dystrophy
Disease course	High fatality	Ranging from very mild to severe	Ranging from very mild to severe
Scaling type	Coarse and large (plate-like)	Large, coarse, plate-like, firmly adherent	Thin superficial and semi-adherent
Scaling color	Gray or yellowish	Dark brown or gray	White or gray
Distribution	Generalized	Generalized; or localize	Generalized
Erythema	Severe	Variable, less pronounced	Variable, often pronounced
Palmoplantar involvement	Synechiae of digits/ keratoderma/ lichenification hypohidrosis	Palmoplantar keratoderma in severe cases, digital sclerodactyly	Palmoplantar hyperkeratosis/ Keratoderma, sclerodactyly
Scalp abnormalities	Boggy scalp, scarring alopecia	Scarring alopecia possible	Tinea amiantacea and patchy cicatricial alopecia
Other skin findings	Prone to skin infections	Sweating is severely impaired	Sweating impaired in childhood
Extracutaneous involvement	Skeletal defects; contractures, failure to thrive; short stature; respiratory failure (restriction of chest wall expansion) vitamin D deficiency rickets	Short stature (if severe); nutritional and vitamin D deficiency rickets	Failure to thrive, short stature, vitamin D deficiency
Risk of death	Very high during neonatal period	Elevated during neonatal period	Present during neonatal period
Histopathology	Compact orthohyperkeratosis extending into dilated hair follicles and pilosebaceous units	Compact orthohyperkeratosis with mild focal parakeratosis and a stratum corneum thickness at least twice that of NBIE. Normal or increased granular layer	Compact hyperkeratosis and moderate increase in stratum corneum thickness. Mild parakeratosis, acanthosis, a normal or prominent granular layer. Mild upper dermal infiltrate, prominent dermal blood vessels
Skin ultrastructure	Multiple vacuoles, lipid droplets and cellular remnants in corneocytes Lamellar bodies in spinous and granular layer cells—absent or abnormal	Prominent cholesterol clefts or crystals in the stratum corneum, lipid droplets in corneocytes and a thin or absent cornified envelope	Abnormal lamellar bodies, which are retained in the corneal layer

Abbreviations: AR, autosomal recessive; HI, harlequin ichthyosis; LI, lamellar ichthyosis; NBIE, nonbullous ichthyosiform erythroderma; TGM, transglutaminase.

BOX 2 Differential diagnosis of lamellar ichthyosis

- X-linked recessive ichthyosis
- Ichthyosiform erythrodermas with collodion presentation
- Ichthyosiform syndromes, such as Sjögren-Larsson syndrome and trichothiodystrophy—associated with neurological problems.

BOX 3 Differential diagnosis of harlequin ichthyosis

- Restrictive dermopathy
- A variant of infantile systemic hyalinosis
- *Stiff skin syndrome (congenital fascial dystrophy)*
- The Neu-Laxova syndrome
- Gaucher type 2 lysosomal disease.

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barrier. Missense mutations in the gene for *ABCA12* lead to HI phenotype by disruption of the epidermal barrier function and failure of desquamation.

Clinical features Harlequin ichthyosis presents as a severe form of collodion membrane at birth which cannot be missed. Many are stillbirths or die within a short span of time. Characteristic skin patterning with ectropion, eclabium and aural and nasal cartilage hypoplasia is seen. If the baby survives, then large plate like scales develops with erythematous deep fissures. Long-term survivors are rare, but if so usually have severe form of ichthyosis and require aggressive medical and nursing care.

Differential diagnosis The distinctive clinical features of HI are unlikely to be confused with the less severe presentation of the collodion baby, the differentials are enumerated in **Box 3**.

Prognosis It is uniformly poor with very few long-term survivors, even amongst the survivors the morbidity is quite high.

Nonbullous Ichthyosiform Erythroderma

Prevalence Occurs in all races across the world and more so in communities where consanguineous marriages are common. Estimated prevalence is 1 in 300,000.

SECTION 48

Common Skin Problems

Etiopathogenesis Nonbullous ichthyosiform erythroderma (OMIM_242100) is considered as hyperproliferative type of ichthyosis caused by epidermal hyperplasia. Expression of hyperproliferative keratins K6/K16/K17 is markedly elevated. Various mutations have been recognized **(Table 4)** accounting for the variable severity.

Clinical features Nonbullous ichthyosiform erythroderma typically presents with collodion membrane in 90% of the cases and in the rest with erythroderma. Subsequently, baby develops generalized scaly erythroderma with fine feathery white scales especially over face and trunk. Lower limbs may develop plate like scales. Other features and a comparison of the more common autosomal recessive congenital ichthyosis (ARCI) are given in **Table 4**. Differential diagnoses are listed in **Box 4**.

Prognosis Nonbullous ichthyosiform erythroderma is a severe form and can result in death in the neonatal period.

EPIDERMOLYTIC ICHTHYOSIS

This entity was earlier referred to as bullous ichthyosiform erythroderma. Its variants include superficial epidermolytic ichthyosis (EI; OMIM_113800) and ichthyosis of Curth-Macklin. It is uncommon with an incidence of 1 case/200,000–300,000 persons in the United States of America. No racial predilection is known.

This condition has an autosomal dominant inheritance with sporadic disease in more than half patients due to de novo mutations. There is a heterozygous mutation of gene coding for Keratin *KRT1* or *KRT10*. Mutations in these keratin genes lead to the formation of defective keratin proteins, which, although still able to incorporate into intermediate filaments, have defective functioning. This leads to skin cell collapse and clinical blistering.

Most children have onset in 1st year of life and present with widespread blistering, increased skin fragility and peeling with underlying erythroderma. There is corrugated ridged scaling in the flexures that may persist as hyperkeratosis after clearing of the erythroderma and blistering. Colonization with *Staphylococcus* and fungi leads to a persistent malodor. Palmoplantar keratoderma may result in fissuring and contractures. Differential diagnosis includes epidermolysis bullosa, staphylococcal scalded skin syndrome, Stevens-Johnson syndrome and XLRI.

Collodion baby Collodion baby is a common morphological term for babies born in a tight, glistening parchment like sheet over the body, with diverse underlying etiology **(Box 5)**. After birth, the membrane desiccates as a result of shift in the environment of baby from amniotic fluid to room air. This leads to shedding of the membrane.

MANAGEMENT OF PATIENTS WITH ICHTHYOSIS

Figure 4 details the suggested approach to a patient with ichthyosis.

Treatment

Nursing care Good nursing care is of utmost importance in management of a neonate with ichthyosis. Most of the mortality is caused by the impaired epidermal barrier, leading to fluid-electrolyte imbalance, dehydration, impaired thermoregulation and loss of nutrients through the skin all of which may culminate into skin failure. Avoidance of low humidity environments and extremes of temperature is crucial. Utmost care should be taken in the prevention and prompt treatment of infections.

Care of skin Education about proper bathing technique is essential as it helps in loosening of the scales. A daily bland bath is advocated and sea salt, sodium bicarbonate, corn or rice starch can be supplemented three times a week in ARCI. Regular and religious application of appropriately chosen *emollients* is

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BOX 4 Differential diagnosis of nonbullous ichthyosiform erythroderma
• Lamellar ichthyosis • Congenital infections including candidiasis • Congenital psoriasis • Netherton syndrome • Immunodeficiency disorders • Trichothiodystrophy (IBIDS) • Neutral lipid storage.

BOX 5 Causes of collodion baby
• Lamellar ichthyosis • Nonbullous ichthyosiform erythroderma • Sjögren-Larsson syndrome • Gaucher disease type 2 • Trichothiodystrophy • Netherton syndrome • Neutral lipid storage disease.

History
• Birth history
 – Prematurity
 – History of collodion membrane
 – Birth complications
 – Failure to thrive
 – Growth retardation
• Onset
• Erythroderma
• Pruritus
• History of consanguinity
• Family history
• Mode of inheritance

Examination
• Cutaneous
 – Collodion membrane
 – Erythroderma
 – Scaling
  ▪ Type
  ▪ Color
  ▪ Distribution
  ▪ Evolution
 – Lichenification
 – Palms/soles involvement
 – Flexures versus extensors
 – Erosions/blisters
 – Hypohidrosis
• Extra cutaneous
 – Hair abnormality
 – Neurological signs
 – Hearing
 – Cryptorchidism
 – Anosmia

Investigations
• Skin biopsy
 – Epidermolytic or nonepidermolytic
 – St. granulosum—absent/ increased
 – TGN activity
 – Staining of filaggrin
• Serum lipoprotein electrophoresis
 – Fast band in XLRI
• STS assay leukocytes/skin fibroblasts-reduced in XLRI
• Chromosome analysis for gene deletions, e.g. Kallman syndrome
• DNA based test
 – FISH
 – Southern blotting
 – PCR

Figure 4 Diagnosis of ichthyosis
Abbreviations: FISH, fluorescent in-situ hybridization; PCR, polymerase chain reaction; STS, steroid thiosulfatase; TGM, transglutaminase; XLRI, X-linked ichthyosis; STS, steroid sulfatase; DNA, deoxyribonucleic acid.

the single most important aspect of subsequent management. In mild-to-moderate cases and generally in IV—light emollient, such as aqueous cream should be used. While in severe cases, concentrated paraffin, cetostearyl alcohol-containing emollients should be used. Glycerol, emollient bath oils, cetomacrogol additives (enhance the antipruritic effect of bath oils) are other alternatives. The basic premise of action of these emollients is that, by forming a lipid barrier over the stratum corneum, they prevent further loss of water and help in the epidermal barrier function.

In addition to these, use of *humectants* like 12% ammonium lactate and 5–10% urea which primarily act as hygroscopic substances and try to extract moisture from the environment and maintain the hydration of the skin may be preferred.

Keratolytic agents These help in debulking the stratum corneum and are particularly useful in retention ichthyosis. These agents aid in separation of keratinocytes and subsequent desquamation. The agents commonly used include 1–5% salicylic acid; and alpha-hydroxy acids (lactic, glycollic, malic, mandelic, citric, pyruvic, gluconic and tartaric acids, 5–10% in an oil, lotion, cream or hydrophilic ointment). Mechanical exfoliation can also be achieved with a loofah while bathing. In LI topical calcipotriol, *N*-acetylcysteine and tazarotene 0.05% gel have produced good results. Keratolytics and topical retinoids are avoided in nonbullous ichthyosiform erythroderma as they may act as irritants in an already inflamed skin. Prevention of sunburn and sunstroke in these children is important.

Systemic retinoids These are used as first-line therapy in severe cases of ichthyosis especially during winters when there is maximum worsening and as bridge therapy in milder cases. It has been used in HI, LI, NBIE and Sjögren-Larsson syndrome. It is generally not recommended in Netherton syndrome and may worsen some patients of EI. Systemic retinoids are not appropriate for IV and may even worsen the associated eczema.

The recommended starting dose of *acitretin* is 0.5–0.75 mg/kg/day (higher doses in younger children). A response is evident within 3 weeks; subsequently it is titrated down to the lowest effective level (0.1–0.5 mg/kg/day as maintenance dose). Intermittent therapy is preferred over continued and long-term treatment in view of the potential toxicity, especially in pediatric age group. Pretreatment baseline skeletal survey is recommended for all patients.

Other therapies In patients with both IV and atopic eczema, topical anti-inflammatory or immune-modulatory preparations may in addition be required to take care of the eczema. Physical therapy is important in HI and some cases of LI to prevent contractures. Prevention and symptomatic treatment of complications like ectropion with artificial tears and lubricants may be required.

Prenatal Diagnosis

Detailed genetic counseling is required for affected families and prenatal diagnostic testing should be offered for any future pregnancies, especially in cases of HI and XLRI.

MORE ON THIS TOPIC

Akiyama M. Updated molecular genetics and pathogenesis of ichthyoses. Nagoya J Med Sci. 2011;73:79-90.

Fleckman P, DiGiovanna JJ. The ichthyoses. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: Mc Graw Hill; 2012. pp. 507-37.

Judge MR, McLean WH, Munro CS. Disorders of keratinization. In: Breathnach S, Cox N, Griffiths C, Burns T. Rook's Textbook of Dermatology. 8th ed. New Jersey: Wiley-Blackwell; 2010. pp. 19.1-65.

Oji V, Tadini G, Akiyama M. Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad Dermatol. 2010;63:607-41.

Prado R, Ellis LZ, Gamble R, et al. Collodion baby: an update with a focus on practical management. J Am Acad Dermatol. 2012;67:1362-74.

Chapter 48.16
Genetic Cutaneous Disorders
Manjyot Manish Gautam

The genodermatoses are a large group of inherited single gene disorders with dermatologic manifestations **(Box 1)**. Since many genodermatoses are rare, the recognition of their skin findings can help in the early detection of these disorders and one can look for other abnormalities which may be associated with these multisystem disorders including malignancies. Early diagnosis of the genodermatosis also helps in timely initiation of appropriate therapy including the precautions that may be required to take in a particular disorder. In this chapter, we shall discuss briefly some of the genodermatoses, not hitherto described in this section.

BOX 1 Classification of genodermatoses

- *Inherited immunobullous disorders:* Epidermolysis bullosa
- *Disorders of keratinization:* Ichthyoses, palmoplantar keratodermas, erythrokeratoderma, follicular keratosis
- *Disorders of skin color:* Albinism, Chédiak-Higashi syndrome, Peutz-Jeghers syndrome, piebaldism, incontinentia pigmenti
- *Neurocutaneous syndromes:* Neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, basal cell nevus syndrome, von Hippel-Lindau syndrome, ataxia telangiectasia
- *Genodermatoses originating from ectoderm:* Ectodermal dysplasia
- *Disorders with defects in DNA repair:* Xeroderma pigmentosum, Bloom's syndrome, Cockayne syndrome
- *Poikilodermatous disorders:* Rothmund-Thomson syndrome, dyskeratosis congenita
- *Connective tissue disorder:* Ehlers-Danlos syndrome, pseudoxanthoma elasticum, Marfan syndrome, cutis laxa
- *Vascular genodermatoses:* Osler's disease
- Porphyrias
- *Disorders associated with immunodeficiencies:* Wiscott-Aldrich syndrome, Omenn syndrome
- *Miscellaneous disorders:* Bazex syndrome, Goltz syndrome, Apert syndrome.

ECTODERMAL DYSPLASIA

These are heterogeneous group of disorders in which there is anatomical or functional impairment of one or more epidermal appendages such as hair, nail, teeth and sweat glands. The most common ectodermal dysplasia (ED) are X-linked recessive hypohidrotic ED (anhidtrotic ED) and hidrotic ED.

Hypohidrotic Ectodermal Dysplasia (Christ-Siemens-Touraine Syndrome)

It is characterized by the triad of absent or reduced sweating, hypotrichosis and defective dentition. Most patients are males and have the X-linked recessive form. However, autosomal dominant (AD) and autosomal recessive (AR) forms also exist. Absence or reduced sweating causes heat intolerance. The patient may present in infancy or childhood with recurrent fever of unknown origin and febrile convulsions. Extreme discomfort can follow exertion, exercise or eating hot foods. Alopecia can also be the first feature to attract attention. There is hypotrichosis with fine, slow growing scalp and body hair; sparse eyebrows and normal eyelashes. Dentition is generally delayed and dental anomalies vary from complete to partial absence of teeth with peg-shaped or conical incisors **(Fig. 1)**. Affected persons show a distinctive facies with frontal bossing, saddle nose, sunken cheeks, thick everted lips, large ears and sparse hair. The skin is smooth, dry, finely wrinkled and appears prematurely aged. Nails are normal in most individuals. Hypoplastic lacrimal and salivary mucus glands can lead to decreased tears, dry mouth, and atrophic rhinitis. Corneal and lenticular opacities have occurred and atopic eczema and asthma are often present. Sexual development is usually normal. Mental retardation is present in 30–50% of cases. Life expectancy is normal or slightly reduced.

Diagnosis

The diagnosis is delayed until the child is old enough and develops hair and teeth abnormalities. Once the characteristic facies and lack of sweating **(Fig. 2)** are evident, the diagnosis is obvious and can be confirmed by sweat test and skin biopsy. The epidermis is thin. The sweat glands are absent or sparse. Hair follicles and sebaceous glands are reduced in number.

Fig. 1 Dental anomalies in a patient with hypohidrotic ectodermal dysplasia
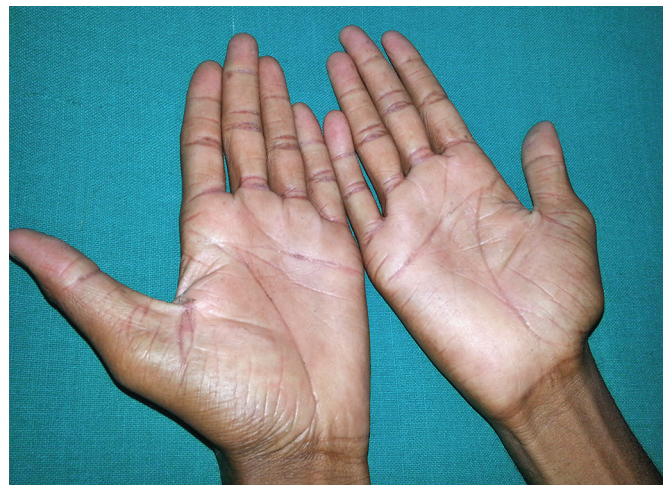
Fig. 2 Dryness of palms due to hypohidrosis in a patient with ectodermal dysplasia

Treatment

Therapy is directed towards temperature regulation. Prevention of hyperthermia is essential which can be achieved by avoiding heat, cool baths, light clothing, wet T-shirts and by air-conditioning home and school environment. Early orthodontic intervention with dentures is necessary. Dry eyes may be treated with artificial tears.

Hidrotic Ectodermal Dysplasia (Clouston Syndrome)

This is a rare autosomal dominant disease characterized by nail dystrophy **(Fig. 3)**, defects of hair and palmoplantar keratoderma. The nails are thickened, discolored, striated and grow slowly. Persistent paronychial infections are frequent. Scalp hair is sparse, fine, brittle and slow growing. Total alopecia can occur. The eyebrows and eyelashes are thin or absent. Body hair is also sparse. Teeth are normal but caries is common. Sweating is normal. Skin tends to be dry and rough. There is diffuse hyperkeratosis of the palms and soles which may be severe with fissuring. The skin may also be thickened over the knees, elbows and knuckles. Additional ectodermal abnormalities may be oral leukoplakia, sensorineural hearing loss, polydactyly and syndactyly. Genital maturity and life expectancy are unaffected. Mental development may be retarded but is often normal.

Treatment

Treatment includes keratolytic agents and emollients. Careful dental prophylaxis, ocular lubrication and controlling onychomycosis are prophylaxis measures.

XERODERMA PIGMENTOSUM

This is a rare disease (AR) characterized by photosensitivity, pigmentary changes and early neoplasia resulting from abnormal DNA repair. There are seven different subtypes of xeroderma pigmentosum (XP) (complementation groups XPA–XPG) and a variant XPV. Both sexes are equally affected. The incidence is 1 in 250,000 billion in Europe and the United States of America and 1 in 40,000 in Japan.

Etiology

There is a defect in the nucleotide excision repair (NER) pathway leading to defective repair of DNA damaged by ultraviolet (UV) radiation.

Clinical Features

Xeroderma pigmentosum involves the skin, eyes and nervous system.

Skin

It may be normal at birth. The first symptoms appear between 6 months and 3 years of age in the form of persistent erythema, acute sunburn, dryness and diffuse freckling of the photo-exposed areas of the body **(Fig. 4)**. With time the lips, conjunctiva, and covered areas of the body are also involved. Multiple telangiectasias are present interspersed among the freckles. Small, white, atrophic macules soon appear giving rise to a mottled appearance. The skin ages, becomes dry, rough and atrophic.

Premalignant lesion like keratoacanthoma and actinic keratoses are common. Basal cell carcinoma (BCC) may appear in the 3rd or 4th year of life. Squamous cell carcinoma (SCC) and melanoma are also common. Angiosarcoma and fibrosarcoma may occur rarely.

Eyes

Ocular manifestations occur in 80% patients and include photophobia, conjunctival xerosis, ectropion, destruction of lower lids, ulceration, pigmented macules on conjunctiva, pterygium, corneal opacities and epithelioma of lids, conjunctiva and cornea.

Central Nervous System

Neurological complications occur in 20% of cases and include mental retardation, areflexia, spasticity, ataxia, sensorineural deafness, dysphasia and abnormal EEG findings.

Systemic Manifestations

Patients have a small stature. There is an increased risk of internal tumors such as medulloblastoma, astrocytoma, and tumors of the lung, stomach, pancreas, uterus, breast, kidneys and testes.

Diagnosis

Photosensitivity, freckled skin and photophobia are quite characteristic of the disorder. Mild and early cases must be differentiated from ordinary freckling, other forms of photosensitivity and premature aging such as progeria, acrogeria, Rothmund-Thomson syndrome, Bloom's syndrome and Cockayne syndrome (CS). Demonstration of the DNA repair defect by unscheduled DNA synthesis (UDS) assay following UV-irradiation of cultured skin fibroblasts confirms the diagnosis (reduced level of UDS). Prenatal diagnosis by amniocentesis is possible.

Fig. 3 Nail abnormalities in a patient with hidrotic ectodermal dysplasia

Fig. 4 Xeroderma pigmentosum
Courtesy: Dr Vishalakshi Vishwanath.

Prognosis

Two-thirds of the patients die before 20 years of age due to metastatic malignancies.

Treatment

No cure is available for XP. Strict photoprotection should be advised once the diagnosis is established. Avoidance of direct sunlight, use of UV-blocking garments, physical sunscreens and change of work schedules should be advised. They should be followed up at regular intervals for early detection of premalignant and malignant lesions which can be treated with topical 5-fluorouracil, cryotherapy, chemical peels, dermabrasion, excision and skin grafting. Oral retinoids can reduce the occurrence of skin cancers. Ophthalmic care includes use of sunglasses, artificial tears, soft contact lenses and corneal transplant.

BLOOM'S SYNDROME (CONGENITAL TELANGIECTATIC ERYTHEMA)

It is a rare AR disorder characterized by photosensitivity, telangi-ectatic facial erythema, stunted growth and predisposition to malignancy. Gene for Bloom's syndrome is located on chromosome 15q26.1. Increased rate of spontaneous sister chromatid exchange (SCE) is characteristic of Bloom's syndrome. There is chromosomal rearrangements and breakage.

Clinical Features

Age of onset—first few weeks of life.

- Growth retardation—both in utero and short stature, normal intelligence
- Erythema and telangiectasia of malar areas and occasionally over dorsal aspect of hands and forearm
- Photosensitivity, bullae, bleeding, crusting of lips after exposure to sunlight
- Characteristic facies—microcephaly with dolichocephaly (longer and narrower head), prominent nose, malar hypoplasia with erythema and telangiectasia
- Males—testicular atrophy and infertility
- Females—reduced fertility
- Recurrent infections—decreased circulating levels of IgA and IgM (chronic respiratory and gastrointestinal tract infection)
- Other features—café au lait macules, clinodactyly, syndactyly, high-pitched voice bronchiectasis, congenital heart disease, high-arched palate, type 2 diabetes mellitus
- Increased incidence of malignancy—leukemia (mean age of development 22 years), lymphoma and gastrointestinal adenocarcinoma

- Life expectancy is reduced. Most common cause of mortality is a neoplastic disease.

Treatment

Treatment consists of symptomatic therapy and photoprotection. Prenatal diagnosis is possible by chorionic villus cell culture.

COCKAYNE SYNDROME (CS)

It is an AR photosensitive disorder characterized by short stature, mental retardation, disproportionately large hands and feet and ocular defects with extensive demyelination. Around 180 cases have been reported till date from the United States, Europe and Japan. Fibroblasts are abnormally sensitive to UV radiation. There is defective transcription-coupled NER and an inability to recover DNA synthesis after exposure to UV radiation. Genes are involved on chromosomes 5 and 10. Patients with CS are classified into three types based on severity of symptoms and age of onset **(Table 1)**.

- Patients have photosensitivity without pigmentary changes, loss of adipose tissue, prominent ears, dental caries and thinning of skin and hair
- *Cachectic dwarfism:* Stooped posture, joint contractures, short stature with extremely thin body habitus and hypogonadism
- Calcification of basal ganglia, demyelination, osteoporosis, pigmentary retinal changes and cataract
- No increase in malignancy in pure CS
- Progressive signs of premature aging occur.

Differential diagnosis includes progeria, Rothmund-Thomson syndrome, and Bloom's syndrome. Prenatal diagnosis is possible by amniocentesis, and chorionic villus sampling (using RNA synthesis recovery technique). Treatment consists of photoprotection and symptomatic relief.

Table 1 Cockayne syndrome (CS)

Features	CS type I (80%)	CS type II	CS type III
Age of onset	2 years of age	At birth	Late onset
Lifespan	2–3 decades	6–7 years	Normal growth and development

MORE ON THIS TOPIC

Bree AF, Agim N, Sybert VP. Ectodermal dysplasias. In: Goldsmith ALA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff l. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. pp. 1691-702.

Palit A, Inamadar AC. Genodermatoses. In: Inamadar AC, Palit A, Ragunatha S. Textbook of Pediatric Dermatology. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2014. pp. 28-88.

Runger TM, DiGiovanna JJ, Kraemer KH. Hereditary disorders of genome instability and DNA repair. In: Goldsmith, LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff l. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. p. 1654-70.

Chapter 48.17
Hair Disorders
Tarang Goyal

Role of hair in humans revolves around social interactions to a major extent and both loss and excess can lead to significant psychological and emotional distress. The first evidence of hair follicle appears at about 10 weeks of fetal age where they develop from epithelial placodes. The subsequent morphological development occurs in 8 consecutive stages. The hair follicle undergoes following stages throughout our lives:

1. *Anagen (growth phase): Scalp hair:* 2–8 years, rest sites vary between 1 month and 7 months
2. *Catagen (involution):* Cessation of mitotic activity by matrix cells and apoptosis
3. *Telogen (resting phase) and exogen (shedding phase):* About 1% of telogen hairs are shed everyday. Scalp hair grows fastest, at the rate of 0.37–0.44 mm/day or 1 cm/month.

ALOPECIA

Alopecia is a general term used for hair loss. It can be scarring and nonscarring, diffuse and focal in each category. Common causes of alopecia in children are discussed here in brief:

Alopecia Areata

It is a complex, chronic organ-specific autoimmune disease mediated by CD8+ T-cells predominantly affecting hair, sometimes nails. Melanogenesis-associated antigens may be one target for the autoantibodies. Family history is positive in 10–42% cases.

Alopecia areata may present as several types: *circumscribed*, *ophiasis* (involving the hairline margins), *sisaipho* (sparing ophiasis areas), *reticular* (innumerable small areas which coalesce), *diffuse*, *totalis* (loss of scalp hair), and *universalis* (loss of whole body hair) **(Figs 1 to 4)**. It may be associated with thyroid diseases, cataract, vitiligo, atopic dermatitis, psoriasis, and Down syndrome. There is usually a positive family history, atopy, and associated nail changes.

Clinically, black dots, cadaver hair, pinot noir, or exclamation mark hair are seen **(Fig. 1)**. *Histopathology* demonstrates *swarm*

Figure 1 Nevus sebaceous of Jadassohn presenting as predominant sebaceous glands and abortive hair follicles on the scalp

Figure 2 Alopecia areata presenting as well-defined patch with *exclamation mark* hair

Figure 3 Ophiasis, a variant of alopecia areata presenting as patch involving the hair margin, starting on occiput and extending 2–2.5 cm wide band over the ear

Figure 4 Multiple patches of alopecia areata involving the scalp

of bees appearance due to T-cell infiltrate around hair follicles. Treatment is listed in **Table 1**.

Trichotillomania

In Greek, the word means *pulling out the hair in madness* (*thrix*, hair; *tillein*, pulling out; *mania,* madness). The incidence is more in girls between 5 years and 12 years. Mostly scalp (sparing of occipital area) is involved, but eyebrows, eyelashes and pubic hair may be involved. Trichotillomania is classified as an impulse control disorder, and characterized by bizarre-shaped, irregular patches of alopecia with rough variably sized hair. The differential diagnoses are alopecia areata and tinea capitis. Treatment consists of hypnosis, behavior therapy and pharmacotherapy clomipramine and selective serotonin reuptake inhibitors.

Tinea Capitis

It is a superficial fungal infection of the skin of the scalp, eyebrows, and eyelashes, with a predilection for attacking hair shafts and follicles, caused by fungi of genera *Trichophyton* and *Microsporum*.

- *Ectothrix*: Arthroconidia develops on the exterior of the hair shaft. Clinically, looks as a gray scaly patch **(Fig. 5)**.
- *Endothrix*: Arthroconidia develop within the hair shaft. Clinically looks as a black dot **(Fig. 6)**.
- Favus, usually caused by *Trichophyton schoenleinii,* produces favus-like crusts or scutula and corresponding hair loss **(Fig. 7)**.

Table 1 Treatment of alopecia areata (AA) in pediatric age group

Limited patchy AA (LPA)	• *< 10 years:* Topical potent steroids ± minoxidil (1–5%) *> 10 years:* Intralesional triamcinolone acetonide (10 mg/mL, 0.05–0.1 mL spaced 1 cm apart) • Topical immunotherapy [squaric acid dibutylester (SADBE)] • Dithranol • Psoralen plus UV-A (PUVA) therapy/excimer laser therapy
Extensive/rapidly progressive AA	• Oral prednisolone, 0.5–0.8 mg/kg/day, tapered over 2 months ± point 1 of LPA • Pulsed systemic corticosteroids
Chronic extensive AA	• Treatment of LPA, plus azathioprine oral

Figure 5 Gray patch type of tinea capitis presenting as scaly patch of hair loss with dull hair

Figure 6 Black dot type of tinea capitis, a noninflammatory type, characterized by short, 1–3 mm broken and lose hair

Figure 7 *Kerion:* Red, oozing, alopecia plaque-studded with pustules

Diagnosis is made by Wood's lamp examination to see fluorescence, KOH (10–20%) examination and Sabouraud dextrose agar incubation at 26–28°C for 4 weeks.

Treatment

- *Oral agents:* Griseofulvin (ultramicrosize 5–10 mg/kg/day), itraconazole (3–5 mg/kg/day up to 200 mg/day), fluconazole (6 mg/kg/day), terbinafine (> 10 kg body weight, ranging from 62.5 mg/day to 250 mg/day depending on weight).
- *Topical agents:* Selenium sulfide, zinc pyrithione, povidone-iodine, ketoconazole, shampoos as well as fungicidal creams or lotions can be used.

Seborrheic Dermatitis

It is a fairly common erythematous scaly eruption involving the face, scalp, and skin folds **(Fig. 8)**. It can present as *infantile form* and *postpubertal form*. It is also called *cradle cap* in infants **(Figs 9 and 10)**. Treatment includes use of oil preparations, and keratolytics to remove scale; a mid-potency topical steroid as 1% hydrocortisone, scalp lotions or foams; shampoos containing selenium sulfide, coal tar, ketoconazole can be used.

Figure 8 Seborrheic dermatitis in a child showing scaling, erythema, ear involvement and yellowish greasy scale

Figure 9 Infantile seborrheic dermatitis showing in addition, face involvement

Figure 10 Cradle cap in a newborn

Figure 11 Albinism with diffuse loss of hair pigmentation

HYPOMELANOSIS HAIR

Traditionally, we describe hypomelanosis into diffuse and localized forms with congenital and later onset diseases occurring in each category.

Premature canities refers to reduction in melanocyte activity within the hair follicles before the accepted physiological age of hair whitening; 20 years in whites and 30 years in blacks. Diffuse hypomelanosis of hair is seen in albinism **(Fig. 11)**, Chédiak-Higashi syndrome, phenylketonuria, and homocystinuria. Diffuse hypomelanosis is also associated with vitiligo, Addison disease, progeria, Down syndrome, and Cri du chat syndrome.

Localized hypopigmentation refers to localized patch of hair due to absent or deficient melanin in a group of neighboring follicles. It presents as white forelock, patchy or as multiple white patches **(Fig. 12)**.

HYPERTRICHOSIS HAIR

Hypertrichosis refers to diffuse or localized patterns of excessive hair growth without evidence of masculinization. It is also

Figure 12 Poliosis or localized hair pigment loss in a group of neighboring hair follicles

Table 2 Causes of diffuse hypertrichosis

Primary hypertrichosis	Hypertrichosis lanuginosa, Ambras syndrome, X-linked dominant/recessive, and prepubertal hypertrichosis
Genetic syndromes	Hypertrichosis with gingival hypertrophy, hypertrichosis with hereditary porphyrias, Cornelia de Lange syndrome, leprechaunism, Rubinstein-Taybi syndrome, and Seip-Berardinelli syndrome
Drug-induced hypertrichosis	*Neonates:* Maternal use of valproic acid, minoxidil, and *infants and children:* Diazoxide, cyclosporine, penicillamine, diphenylhydantoin, minoxidil
Systemic disease associated hypertrichosis	Anorexia nervosa, dermatomyositis, malnutrition, hypothyroidism, and congenital adrenal hyperplasia

Figure 13 Woolly hair nevus in a child

categorized into diffuse and localized forms. Causes of diffuse hypertrichosis are listed in **Table 2**. Localized hair growths are associated with nevi **(Fig. 13)**, tumors, or dermal dysplasia. A tuft of hair over lower back suggests spina bifida.

Hirsutism It is defined as excessive hair growth in women in those parts of the body where terminal hair does not normally occur or is minimal, e.g., a beard or chest hair. It refers to a male pattern of body hair (androgenic hair) and it is therefore primarily of cosmetic and psychological concern.

MORE ON THIS TOPIC

Bennàssar A, Ferrando J, Grimalt R. Congenital atrichia and hypotrichosis. World J Pediatr. 2011;7:111-7.

Mirmirani P, Huang KP, Price VH. A practical, algorithmic approach to diagnosing hair shaft disorders. Int J Dermatol. 2011;50:1-12.

Moreno-Romero JA, Grimalt R. Hair loss in infancy. G Ital Dermatol Venereol. 2014;149:55-78.

Suga H, Tsunemi Y, Sugaya M, et al. Hair shaft abnormalities in localized autosomal recessive hypotrichosis 2 and a review of other non-syndromic human alopecias. Acta Derm Venereol. 2011;91:486-8.

Chapter 49.1

Assessment of the Locomotor System

Jayanth Sundar Sampath, Harish S Hosalkar

The human locomotor (musculoskeletal) system is an extremely complex system with series of structural links between bones and joints that have led to an erect posture of the *Homo erectus*. This system consists of bones, muscles, ligaments, cartilage, tendons, joints and other structures that together provide structure and support to the body, in addition to coordinating movements and propulsion. Assessment of the musculoskeletal system in a child can be a *screening assessment* (designed to rule out certain conditions which may be quite subtle at the time of assessment but could lead to later disability) or a *focused examination* (an assessment based on the particular presenting complaint of the child). Examples of clinical scenarios applicable to these two categories are summarized in **Table 1**.

HISTORY TAKING

Typical presenting complaints that prompt a clinic visit include pain, limp, deformity, swelling of one or more joints, weakness, and fatigue. History of present illness should focus on symptom onset, progress and duration. Pain should be described in terms of location, severity, frequency, aggravating/relieving factors, associated symptoms, diurnal variations (night pain and sleep disturbance), and response to painkillers. A history of trauma should be enquired into but may be coincidental to the pain. Traumatic pain typically starts immediately after the incident, worsens progressively over the next few days and then may settle depending on the etiology. Pain due to a fracture is typically severe

Table 1 Examples of common clinical scenarios in assessment of locomotor system

Screening assessments	Focused examination
• Neonate with risk factors for developmental dysplasia of the hip [DDH or congenital dislocation of the hip (CDH)]	• Hip pain/limp in a 5-year old
• Delayed walking in a child aged 12–18 months	• Back pain in a 12-year-old boy who plays regular sports
• Children aged 1–5 years with normal variants such as physiological knock-knees, bow legs, intoeing gait and flatfeet	• Atraumatic swelling of the knee in a 3-year-old girl
• Scoliosis screening in adolescent girls	• Swollen ankle after a fall downstairs

and the patient will be unable to bear weight in most fractures involving the lower limb.

The relationship of symptoms to activity is significant. If pain is aggravated by activity and relieved by rest, the cause is typically *mechanical* (due to damaged ligaments, cartilage, muscle, etc.). Pain present at rest and particularly at night is suggestive of more serious causes such as infection or a neoplastic process.

Family History

History of similar complaints in family members, the number, age and current health of all siblings and death of siblings/first degree relatives must be recorded. Orthopedic disorders with an inherited element include developmental dysplasia of the hip (DDH), clubfoot, scoliosis, various genetic syndromes including skeletal dysplasias, neuromuscular disease and osteogenesis imperfecta.

Antenatal and Birth History

Breech position is associated with higher risk of DDH and positional foot deformities. An abnormal lie, large baby and difficulties during delivery may predispose to obstetric brachial plexus injury and birth fractures. Premature and very low birthweight babies have a higher risk of cerebral palsy. Invasive procedures in the neonatal period (umbilical artery catheterization) and neonatal intensive care unit (NICU) admission and invasive procedures may predispose the baby to musculoskeletal infections, most commonly septic arthritis of the hip.

Growth and developmental history is important when there is a history of motor delay, psychomotor/cognitive impairment or behavioral problems.

ORTHOPEDIC EXAMINATION

The examination of a child begins with carefully observing the way the child walks into the room. Children under the age of about 4 years walk with an immature gait pattern characterized by a wide base of support (feet separated by a greater distance than normal) with short, quick steps. This is physiological and resolves with gradual maturation of the neuromuscular control mechanisms by the age of about 5–6 years.

Gait

Human walking follows a repetitive pattern called the gait cycle. The gait cycle can be divided into two parts, namely (1) the *stance phase* when the lower limb is in contact with the ground and (2) the *swing phase* when the limb is lifted off in order to advance the body forwards. Stance phase accounts for about 60% of the gait cycle and the swing phase contributes about 40% **(Fig. 1)**.

Asking children to walk on the toes and on the heel distracts their attention and may help to unmask the natural walking pattern. Common abnormalities of gait are summarized in **Table 2**.

Examine the Spine

The child is asked to stand and bend forwards. The spine is best examined from behind. The shoulders and posterior iliac crests

Figure 1 Phases of the gait cycle for the right leg. In *stance phase*, the foot is in contact with the ground and the limb supports the weight of the body. In the *swing phase*, the limb advances forward off the ground (*Reproduced with permission from: Elsevier*)

Table 2 Abnormalities of the gait

Gait abnormality	Description
Antalgic gait	Painful limb; stance phase reduced
Short limb gait	During stance phase on the shorter leg, the ipsilateral shoulder dips down allowing the foot to reach the floor
Trendelenburg gait	Due to a painful hip or weak hip muscles, the entire body sways towards the affected side during stance phase
Intoeing/Out-toeing	The affected foot points inwards/outwards in relation to the direction of walking (normal 10–15° outwards)
Toe-toe gait	The heel never touches the ground in the stance phase (also called toe walking or equinus gait)
Circumduction gait	The hip is abducted and externally rotated during swing phase to allow ground clearance (due to stiff knee)
Steppage gait	Compensatory excessive flexion of the hip and knee in children with equinus contracture of the ankle (high-stepping gait)

Figure 2 Adams forward bending test for scoliosis
(*Source: Dr Thomas Kishen, Bengaluru*)

should be at the same level. When bending forwards, the spine must then lie on a straight line. Any prominence of one side of the thorax could indicate a structural scoliosis. This is called the *Adams forward bending test* **(Fig. 2)**. The midline is inspected for a hairy patch which may be the only sign of an underlying spinal dysraphism.

Examine the Limbs

Inspecting both legs from the front helps to assess deformities in the coronal plane (genu valgum/genu varum) and from the side reveals flexion contractures of the hip or knee. Hip flexion contractures are usually masked by compensatory hyperlordosis of the lumbar spine.

The child is then asked to climb onto the examining couch, a clinical test of strength and coordination. Babies must be placed on a firm surface when examining the hips. The child is initially examined in the supine and then the prone position. All the joints of both lower limbs are examined in a systematic manner following the standard orthopedic dictum of *Look, Feel, Move, and Measure* (inspection, palpation, joint range of motion, measurement of limb length and circumference).

The orthopedic examination is completed by assessing the neurological function of all four limbs or the affected area. Distal pulses must be felt for, particularly following injuries to the limbs.

Assessment of Deformity

It is important to look for and describe deformities correctly. An abnormal deviation of the limb towards the midline is called a *varus deformity* **(Figs 3A and B)** and a deviation away from the midline is called a *valgus deformity* **(Fig. 4)**. The location of the deformity is described in terms of its anatomic term such as cubitus (elbow), coxa (hip), genu (knee) or pes (foot). The magnitude of the deformity may be quantified in degrees using a hand-held goniometer. It is also important to document whether the deformity can be passively corrected by applying gentle pressure (fixed or flexible deformity).

Screening Assessment of a Limping Child

The *pediatric Gait, Arms, Legs, and Spine* (pGALS) examination **(Table 3)** is quick to perform, acceptable, and a validated musculoskeletal screening examination tool in school-aged children.

FOCUSED ASSESSMENTS: COMMON CLINICAL SCENARIOS

A 6-Week-Old Girl with a Hip Click Noticed during Nappy Change

Clicky hips have a variety of causes, some of them are self-limiting (popping iliopsoas tendon over the hip capsule or ligamentum teres gliding within the hip joint) and others require immediate attention (dislocated hip). It is possible to distinguish between the two through specific points in the history and examination.

Presence of oligohydramnios, birth order (first born female babies), breech presentation, developmental history (neurological

Figures 3A and B (A) A 12-year-old girl with bilateral Blount's disease showing genu varum deformity of knee; and (B) X-ray of the same girl

Figure 4 Bilateral genu valgum deformity

Table 3 Pediatric gait, arms, legs and spine (pGALS) examination for the limping child

Screening question	Do you have any pain or stiffness in your joints, muscles, or back?
Gait/general	Observe the child walking. Ask the child to walk on his or her tiptoes and heels
Arms	Examine all joints of the both arms from the shoulders to the small joints of the hands. Check for supination-pronation of the forearm. The child is asked to lift both arms above the shoulder and place the palms behind the head
Legs	Feel for effusion of the knee
	Ask the child to bend and then straighten your knee and feel for crepitus
	Apply passive flexion (90°) with internal rotation of hip and then external rotation
Spine	Observe the spine from behind
	Ask the child: Can you bend and touch your toes? Observe the curve of the spine from the side and behind

disorders such as arthrogryposis result in teratologic dislocation of the hip) and family history of DDH in first degree relatives. Associated features of DDH include congenital muscular torticollis and metatarsus adductus. The physical examination should include both Barlow and Ortolani tests to rule out DDH. These tests are further detailed in the Chapter on Developmental Dysplasia of the Hip.

The Barlow-Ortolani maneuvers are useful during the neonatal period but are not as reliable in older children. Beyond 3–6 months of age, secondary contractures of the capsule, ligaments and adductor muscles cause limitation of hip abduction. Diagnosis of DDH in older children is also detailed in Chapter on Developmental Dysplasia of the Hip. In children of walking age, DDH is typically diagnosed through a painless limp which is noticed by the parents or in bilateral DDH, a waddling gait or lumbar hyperlordosis may become apparent (compensatory to the hip flexion contracture).

A 20-Month-Old Girl Presents with Bowed Legs (Genu Varum)

History

It is important to establish when the deformity was first noticed and whether there has been any progression over a period of time. Genu varum is usually painless. The birth and developmental history are typically normal, though in cases of skeletal dysplasia there may be short stature and growth retardation. History of similar complaints in family members may be significant in this context. Dietary history is relevant with regard to nutritional rickets.

Examination

Height, weight and head circumference must be recorded. Clinical features of rickets such as expansion of the long ends of bones (wrists) may be present. The spine, hips and arms are examined to rule out the possibility of skeletal dysplasias such as spondyloepiphyseal dysplasia. The child may have a waddling gait. The affected limb is inspected to assess the exact location of the deformity. A sharp angulation in the upper tibia, which is unilateral, may indicate Blount's disease. A more uniformly distributed genu varum which is bilateral and symmetrical is usually *physiological bowing* in an 18-month-old child **(Figs 5A and B)**. This usually corrects to a neutral alignment by the age of 24 months. The legs then develop a *physiological genu valgum (knock-knees)* which may persist up to the age of 5 years. The normal tibiofemoral angle in adult is 5–7° of valgus alignment.

A 3-Year-Old Boy with Intoeing Gait and Frequent Falls

History

It is fairly common for children in this age group to trip and fall frequently but this could also be the first indication of an underlying disorder such as a neuromuscular disorder or cerebral palsy. One should look for other features of development delay such as retention of primitive reflexes and cognitive delay. In most toddlers, the intoeing gait is first noticed by grandparents, neighbors or staff at the nursery/playgroup. Parents are usually aware of whether the problem is unilateral or bilateral and whether it is improving. Intoeing gait that is bilaterally symmetrical indicates a physiological normal variant in this age group. Birth and developmental history are relevant.

Examination

To properly examine a toddler who is going through the *terrible twos* can be challenging. It requires considerable patience and experience. It is best to elicit most of the physical signs by inspection and observing the child's gait pattern. The parent is then asked to walk the child around the waiting area or a quiet corridor. The child's gait pattern is observed for any asymmetry. By the age of about 30 months, most children have relatively symmetric gait with greater time spent in stance phase (approximately 60%). Occasional toe walking, if present, should be recorded. *Foot progression angle* is the angle made by the long axis of the foot with an imaginary straight line drawn on the floor along the line of walking **(Fig. 6)**.

Intoeing gait occurs principally at three levels, namely (1) the femur, (2) tibia and (3) foot. The relative alignment of the lower limb in the axial plane is called *torsional profile* and must be assessed in every child. This examination is carried out in the prone position. The degree of internal and external rotation of the hip indicates the amount of femoral anteversion. *Femoral version* is the angle made by the proximal femur in relation to the distal femur. At birth, the femoral anteversion angle is approximately 60°. It reduces over the first 2 years of life to the normal adult anteversion of 10–15°. The process of remodeling of the femur may take up to 5 years. Persistent femoral anteversion causes increased internal rotation and reduced external rotation in the hip **(Figs 7 and 8)**.

Tibial torsion (rotation of the tibia along its axis) is internal at birth and becomes external over the first 2–3 years of life. Internal tibial torsion is best assessed by recording the *thigh-foot angle* **(Fig. 9)**. Physiological foot deformities such as metatarsus adductus can also cause intoeing gait.

Figures 5A and B An 18-month-old girl with typical physiological bowing (A) from front; and (B) from behind
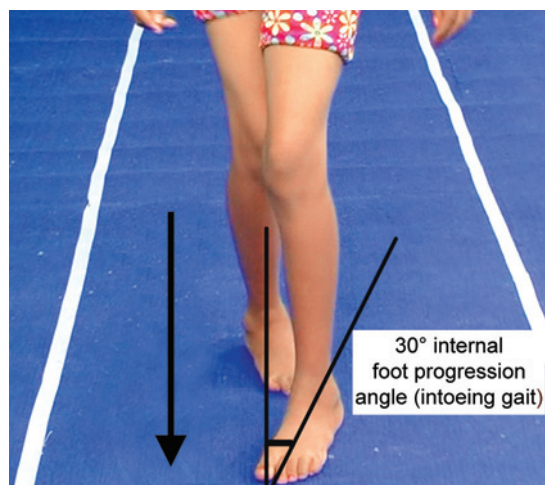
Figure 6 Foot progression angle

Figure 7 Increased internal rotation of the hip in the prone position in a child with increased femoral anteversion and intoeing gait
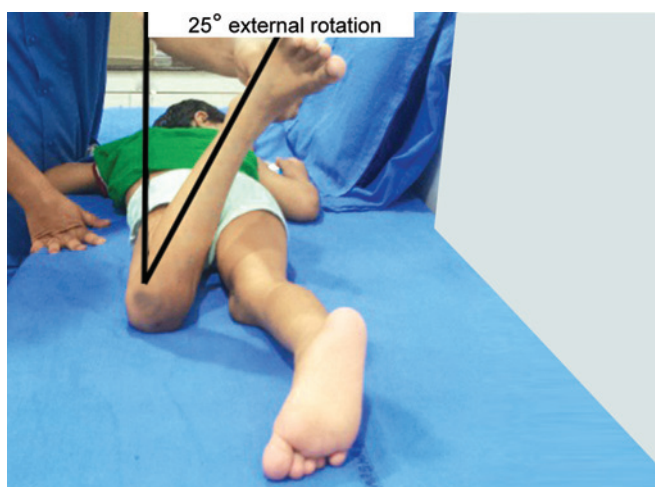
Figure 8 Reduced external rotation in a child with intoeing gait

Figure 9 Thigh-foot angle measurement

A 3-Year-Old Boy with an Atraumatic Limp of 24-Hour Duration

The most common diagnosis in this scenario is *transient synovitis of the hip* (irritable hip) but more serious causes such as septic arthritis of the hip, osteomyelitis of the femur, juvenile idiopathic arthritis (JIA), etc. must be considered during assessment. In the age group of 4–7 years, Perthes disease must be considered in the differential diagnosis of a painful limp.

History

Children develop a mature, reproducible gait pattern at around 7 years of age. In children younger than 7 years, it is important to ascertain whether there has been a recent alteration in the child's walking pattern. The onset, duration, progression and severity of the pain/limp provide important clues as to the diagnosis. In transient synovitis, the child typically has been limping for a day or two, though they may stop walking altogether for a brief period. There may be a history of viral illness in the preceding 1–2 weeks. A low-grade pyrexia may be present but the child typically appears well. Bone or joint infection has a sudden onset with rapid progression associated with systemic symptoms and high-grade fever (> 38.5°C). The child is unable to weight bear. Children with JIA have recurrent bouts of limping and pain in the hip or knee lasting several months, with periods of normal activity in between. Acute leukemia and tuberculosis (TB) osteomyelitis are also a known cause of an atraumatic limp in this age group. Loss of appetite, loss of weight and history of contact with a patient of TB must be looked for.

Examination

The gait of the child is observed. Children with transient synovitis usually walk into the examination room but may have a slight limp, whereas a child with septic arthritis will be carried or brought in a wheelchair. The limb is usually in an attitude of slight flexion, abduction and external rotation at the hip thus maintaining the hip capsule in maximal relaxation. Transient synovitis causes mild pain during terminal ranges of passive movement. In septic arthritis, the child resists any movement of the affected hip. Bony tenderness of the femur and tibia indicates osteomyelitis or a fracture. Restriction of internal rotation of the hip is an early and sensitive sign of hip pathology.

A 5-Year-Old Boy with a Painless Flatfoot

Painless and flexible flatfoot is a physiological normal variant that does not require any treatment. But, a flatfoot may be first sign of intrinsic foot pathology such as tarsal coalition or neurological disorders (spinal dysraphism).

Figures 10A and B (A) Normal hindfoot on the right and valgus hindfoot on the left side; (B) On tiptoeing, the right foot goes into varus and the left foot (fixed deformity) remains in valgus

History

In physiological flatfeet, the child is asymptomatic and first noticed by relatives or teachers. A painful flatfoot should always be investigated further. If pain is present, the nature and severity of pain helps differentiate mechanical problems from sinister pathology. Night pain is always significant, as is activity limitation or limping.

Children in this age group (4–7 years) frequently suffer from *bilateral calf pain* in the evenings. This has been termed *growing pains*, though the exact cause is yet to be fully understood. It is a benign and self-limiting condition, which requires symptomatic treatment.

Examination

A screening examination of the entire body is first carried out. pGALS is a comprehensive and quick method of assessing the entire musculoskeletal system in less than 5 minutes. The feet are observed from behind the patient. The child is asked to stand on his toes. The hindfeet are normally in slight valgus at rest and move into varus on tiptoeing. In the presence of any bony pathology such as tarsal coalition or if there is a neuromuscular disorder, the hindfoot (heel) remains in valgus due to stiffness in the subtalar joint or due to a fixed valgus hindfoot deformity. Hindfoot varus at rest is also an indicator of foot deformity.

In the typical child with a flexible flatfoot, the hindfoot moves into varus on tiptoeing **(Figs 10A and B)**. Passive range of movement in the ankle and subtalar joints is within normal limits. There is loss of the medial longitudinal arch but the arch restores on tiptoeing. The metatarsophalangeal joint of the big toe is dorsiflexed which also restores the arch (Jack test).

Examination of the spine is essential since children with unilateral foot deformity may have otherwise asymptomatic intraspinal lesions such as a cord tumor or spinal dysraphism.

A 12-Year-Old Boy with Left Knee Pain and Limp for 2 Months

Knee pain is common in the adolescent age group. In the vast majority of cases, it is benign and self-limiting caused by the pubertal growth spurt and mechanical changes within the patellofemoral joint (called *anterior knee pain*). The clinical evaluation must focus on ruling out less common but serious causes which may require emergent treatment. Referred pain from the hip must be considered in every child presenting with knee pain.

History

The onset, duration and progression of pain provide important clues. Anterior knee pain has typically been present for several months without any antecedent history of trauma. The pain is aggravated by exercise and relieved by rest.

Night pain should raise the rare possibility of an osteogenic sarcoma or other bone tumors which occur around the knee. Mechanical symptoms such as locking and *giving-way* of the knee following trauma point to tears of the menisci or cruciate ligament. Routine birth, development, personal and social history is typically normal; recent growth spurts or weight gain may indicate hormonal imbalance [risk of slipped capital femoral epiphysis (SCFE)].

Examination

The patient may be obese with underdeveloped genitalia for age (increased risk of SCFE). The gait in a child with SCFE shows an antalgic pattern with a Trendelenburg type of limp (swaying of the body towards the stance phase limb—left leg in this case). The leg may be externally rotated when lying down and an external foot progression angle may be present when walking.

The knee joint is checked for active and passive range of motion. Small amounts of effusion in the knee can be appreciated by squeezing the suprapatellar pouch and looking for fullness over the medial aspect of the knee. The medial, lateral and patellofemoral joints are palpated for crepitus and tenderness. Swelling or bony tenderness around the knee indicates possible lumps or tumors.

The hip joints must be examined in every case of knee pain. Painful or restricted internal rotation is an early sign of SCFE.

IN A NUTSHELL

1. Evaluation of the locomotor system in a child could be a *screening examination* or a *focused assessment* based on the clinical scenario.
2. Detailed history and systematic physical examination of the affected joint(s) are crucial in generating a differential diagnosis.
3. There are a number of abnormal gait patterns in children, knowledge of which can direct the examination towards the affected joint.
4. The *pediatric Gait, Arms, Legs, and Spine* is a quick and useful assessment tool in the evaluation of school-going children.
5. Hip pathology must also be suspected in children with knee pain.

MORE ON THIS TOPIC

Bracken J, Ditchfield M. Ultrasonography in developmental dysplasia of the hip: what have we learned? Pediatr Radiol. 2012;42:1418-31.

Burnham JM. Inflammatory diseases and bone health in children. Curr Opin Rheumatol. 2012;24:548-53.

Fardeau M, Desguerre I. Diagnostic workup for neuromuscular diseases. Handb Clin Neurol. 2013;113:1291-7.

Foster H, Kay L, May C, Rapley T. Pediatric regional examination of the musculoskeletal system: a practice- and consensus-based approach. Arthritis Care Res (Hoboken). 2011;63:1503-10.

Gill KG. Pediatric hip: pearls and pitfalls. Semin Musculoskelet Radiol. 2013;17:328-38.

Sirisena D, Begum H, Selvarajah M, Chakravarty K. Musculoskeletal examination—an ignored aspect. Why are we still failing the patients? Clin Rheumatol. 2011;30:403-7.

Woolf AD, Akesson K. Primer: history and examination in the assessment of musculoskeletal problems. Nat Clin Pract Rheumatol. 2008;4:26-33.

Chapter 49.2
Osteomyelitis
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Osteomyelitis (*osteon*, bone; *myelo*, marrow; *itis*, inflammation) as the term implies, refers to the infection and inflammation of the bone and bone marrow. Over the last few years, the incidence of osteomyelitis has decreased in developed countries, but we still continue to deal with both childhood and adult osteomyelitis in India. Osteomyelitis in combination with acute septic arthritis is a serious condition and requires emergent attention especially in children to prevent complications and often disastrous sequelae.

EPIDEMIOLOGY

The exact incidence of osteomyelitis has tremendous geographic variation. The incidence in the developed countries is considered to be around 1:20,000 while in India and other developing countries, the incidence is said to be around 5:10,000 though detailed population studies are not available for developing countries. In addition, a number of cases of osteomyelitis in children may get misdiagnosed as soft tissue infections and hence a true idea about the incidence and prevalence is not available. Boys are more commonly affected than girls and more than 50% of all cases occur before the age of 5 years. The long bones are more commonly involved though any bone as such can be involved with osteomyelitis. The mortality of acute bacterial osteomyelitis was approximately 20–30% a few decades back, which has now decreased to less than 1% with the advent of higher antibiotics and appropriate early surgical management. However, the morbidity of sequelae and complications of osteomyelitis are still relatively high at around 5–6%.

PATHOGENESIS

Osteomyelitis could be categorized into three types: (1) acute hematogenous osteomyelitis (AHOM), (2) osteomyelitis secondary to contiguous spread of infection following trauma or through puncture wounds and surgery, and (3) osteomyelitis secondary to vascular insufficiency.

Acute hematogenous osteomyelitis (AHOM) occurs *because of bacteremia* with resultant seeding of the metaphyseal blood vessels due to sluggishness of blood flow in the U-shaped bends of the blood vessels. The basic pathology of AHOM is involvement of the metaphyseal region with a subperiosteal collection and abscess formation followed by avascularity of the subperiosteal bone which derives its blood supply from the periosteum and subsequent sequestrum (dead bone) formation.

Staphylococcus aureus is the most common organism to cause acute hematogenous osteomyelitis (AHOM) probably because of the capacity to express bacterial adhesions to promote attachment to the extracellular bony matrix. AHOM is the most common type of osteomyelitis in children and has a very high chance of morbidity. It can also occur due to contiguous spread from septic arthritis in joints where the epiphysis is intra-articular, for example, the hip, shoulder and proximal radioulnar joints.

Osteomyelitis can also occur *due to direct inoculation* from puncture wounds, during surgery or intramuscular/intra-articular injections. Intramuscular ones can occur after immunization due to improper sterility and occurs more commonly when immunization is performed on the anterolateral aspect of the thigh since the gluteal musculature is much bulkier than the anterolateral thigh.

Osteomyelitis also can occur after open fractures due to direct contamination from the surroundings.

The third type of osteomyelitis can occur *due to vascular insufficiency*. In diseases like sickle cell anemia, there occur vascular infarcts along the shaft of the bone with resultant avascular segments which act as good media for bacterial growth. Although avascularity itself is not an infection, there can be seeding and this can result in diaphyseal osteomyelitis which is typically seen in sickle cell disease.

ETIOLOGY

The most common organism causing AHOM in children is *S. aureus* which accounts for around 70–90% of all cases. Methicillin-sensitive *S. aureus* (MSSA) is still the most common organism in community acquired AHOM while methicillin-resistant *S. aureus* (MRSA) is becoming increasingly common in the hospital-acquired setting. The other organisms causing AHOM are *Streptococcus agalactiae* or enteric Gram-negative bacteria especially in neonates and infants. In older children, *Streptococcus pyogenes, Streptococcus pneumoniae* and *Kingella kingae* are increasingly seen. *S. pyogenes* is relatively common in toddlers and preschool children and the characteristic feature is higher fever and white blood cell (WBC) counts than those seen in *S. aureus* AHOM. Also, they seem to have a recent history of varicella infection though the exact reason for this association is not known.

Kingella kingae is also becoming increasingly common as a pathogen for AHOM. It occurs usually in day care centers and crèches and is preceded by an upper respiratory tract infection. The child is usually not so toxic after *K. kingae* infection as compared to AHOM from staphylococcal or streptococcal infection.

Organisms causing osteomyelitis in sickle cell disease characteristically include capsulated organisms: *Salmonella, Pneumococcus* and *Haemophilus influenzae.* Organisms causing infection after puncture wounds include *Pseudomonas*, anaerobes and *S. aureus*. The other less commonly involved organisms in AHOM are *H. influenzae, Shigella, Escherichia coli* and some fungi.

CLINICAL FEATURES

The child with AHOM presents with severe pain in the affected limb, along with high-grade fever and irritability, usually of less than 2-week duration. There is great reluctance to use/move the affected limb and in older children, they present with inability to bear weight on the affected limb. Local examination reveals a swollen tender limb, with local warmth, redness and sometimes a fluctuant swelling. On detailed examination, one can usually feel a bony swelling or swelling along the shaft of the bone, though this may be difficult in an acutely painful child.

Sometimes, the child may present with subacute or chronic features, in the form of a discharging sinus formation, a bony deformity, or a pathological fracture. All these are signs of chronic osteomyelitis formation and as such they need a different type of management.

The signs and symptoms may be a bit masked in children who are immunosuppressed due to any cause and also in those who have been inadvertently given antibiotics before drainage of the pus. This results in emergence of resistant strain as well as infection by slow-growing atypical organisms like *K. kingae* and fungi.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for AHOM includes any cause of acute painful limb such as scurvy, trauma, physeal injuries and bony infarctions as in sickle cell disease.

INVESTIGATIONS

Radiological Investigations

Plain radiographs The role of plain radiographs in the diagnosis of early bone and joint sepsis is often undervalued. It is because the most sought after change is osteopenia or bone lysis, which often takes many days or sometimes weeks to develop. Deep soft tissue swelling with obliteration of fat plane may be the earliest radiographic evidence. Unlike older children, radiographic changes appear early in neonatal age group. The thin periosteum ruptures easily, and osteolytic lesions, soft tissue swelling and periosteal elevation are often seen within days of onset of infection. Erosion of the cortex, cavitation in the metaphysic or epiphysis can often be seen even earlier. However, plain X-rays can be normal in early stages of osteomyelitis and waiting for radiographic changes to appear before making a diagnosis may invite complications.

Ultrasonography It is useful in places where magnetic resonance imaging (MRI) is either not available, not affordable, or not feasible (in a very sick patient). Ultrasound can detect the soft tissue collection as well as its extent. It is not useful to detect intramedullary changes as well as in deeper tissues like the pelvis. Ultrasound is also difficult to perform in an uncooperative child and is operator-dependent.

Radionuclide scans These scans are helpful modalities for the early detection of AHOM. These become positive in only about 48–72 hours after the onset, are relatively quick and may not require anesthesia or sedation as in MRI. It is of great help in suspected multifocal osteomyelitis. However, the main disadvantage of bone scan is the high amount of radiation hazard. Also, bone scan is good only for the diagnosis of osteomyelitis, its use in the surgical planning is limited as it does not provide the orthopedic surgeon with any clue about the exact location and extent of the soft tissue collection.

Magnetic resonance imaging Over the last two decades, MRI has emerged as the primary diagnostic modality for osteomyelitis. MRI provides excellent resolution of soft tissues and bones and is useful for detecting intramedullary collection as well as soft tissue abscesses. Involvement of the deeper tissues as in pelvic osteomyelitis and vertebral osteomyelitis can be easily detected. In addition, it provides an excellent method for surgical planning of drainage since the exact size, location and extent of collection can be studied in great detail. The disadvantages of MRI include its high cost, nonavailability in all centers, the need for sedation or anesthesia in younger kids as well as difficulty in assessing involvement in multiple places.

Hematological Investigations

Hematological investigations include WBC count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). CRP is elevated in almost 98% of all cases and it reaches a peak by around 48 hours of admission. ESR is elevated in about 80% of cases and it reaches a peak about 4–7 days after admission. Hence, repeat work-up 7 days after the debridement may show elevated ESR despite clinical improvement. WBC count is most unpredictable among the three and may be elevated in about 60% of all cases. Blood culture is positive in almost 80% of all cases, especially in those who have not been given antibiotics before sampling.

MANAGEMENT

Management of AHOM requires a multidisciplinary approach, which includes an orthopedic surgeon preferably comfortable handling pediatric patients, an intensivist, infectious diseases specialist, microbiologist and musculoskeletal radiologist. The treatment should be prompt and includes early surgical drainage of the collection, not just of the soft tissue collection, but also of the intramedullary abscess, as well as medical management of the sepsis with the help of appropriate dose and duration of antibiotic therapy.

Surgical Management

Early surgical intervention in AHOM, when indicated, provides best outcomes. The role of surgery is to improve the local environment by removing infected devitalized bone and soft tissue, decompressing a large abscess cavity and allowing for antibiotics to reach the abscess cavity. It involves open surgical drainage and debridement of the collection, not just of the soft tissue and subperiosteal collection but also of the intramedullary collection. It may be required to create drill holes and/or a cortical window in the bone in order to release the collection and decompress the marrow **(Figs 1A to C)**. The bone marrow cavity should be thoroughly debrided and curetted and a thorough wash needs to be given using copious amounts of normal saline. In severe cases, antibiotic impregnated cement beads can be inserted in the cavity for local sustained and continued release of antibiotics.

Once chronic osteomyelitis develops, it is necessary to remove the sequestrum (i.e., the dead bone) for eradication of infection **(Figs 2A to C)**. This is an important step and the exact location and size of the sequestrum has to be studied in detail preoperatively to ensure complete removal of the same.

Figures 1A to C (A) Clinical photograph of a 13-year-old boy showing swelling and redness over the right lower leg. He was operated previously a few years back for some fracture, of which the details were not known; (B) MRI images of the same child showing significant intramedullary (blue arrow) and subperiosteal (white arrow) collection; (C) Clinical intraoperative photograph showing the cortical window (arrow) created to drain the intramedullary collection
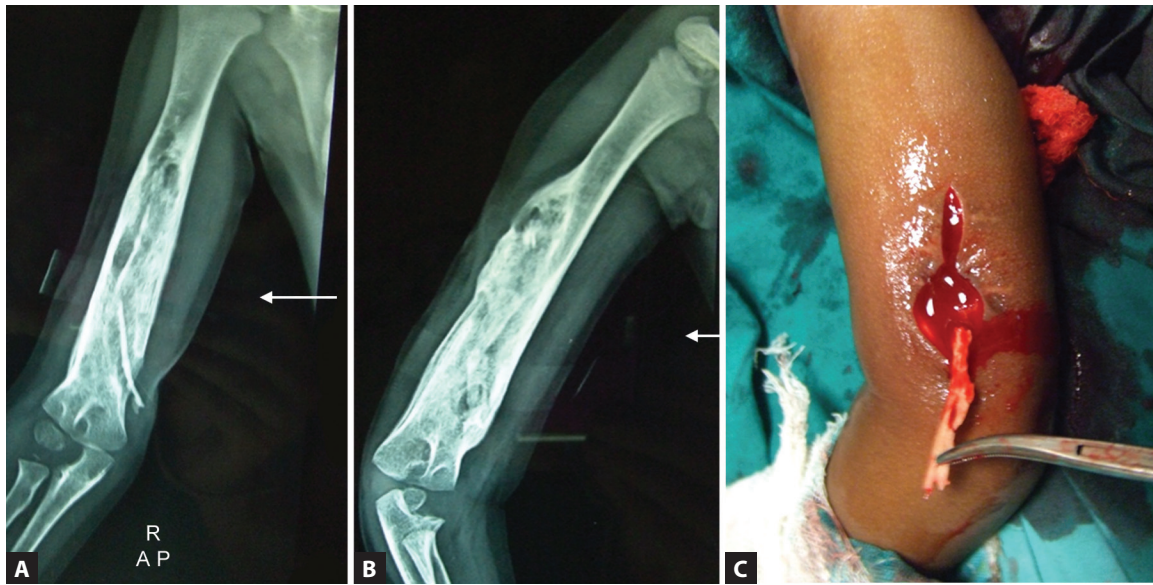
Figures 2A to C (A and B) Anteroposterior and lateral plain radiographs of the arm of a 7-year-old girl with chronic discharging sinus over the medial side of the elbow with swelling over the entire arm. Plain radiographs show the presence of a large sequestrum (arrow); (C) Intraoperative photograph of the same child showing excision of a large sequestrum through the medial wound

Medical Management

Successful treatment of AHOM relies heavily on selection of an appropriate antibiotic depending on the age of the patient and the clinical scenario. Initially, empiric broad-spectrum antibiotics may be started till culture is obtained. For community-acquired infections in children, ampicillin-cloxacillin or amoxicillin-clavulanate are appropriate antibiotics. Vancomycin needs to be given for suspected MRSA. In very young children and neonates, vancomycin along with third-generation cephalosporins can cover both gram-positive and gram-negative organisms. Linezolid is the drug of choice for hospital-acquired infections. Children with sickle cell anemia are more prone to *Salmonella* infections and hence ceftriaxone may be used as the drug of choice.

The duration and type of antibiotic therapy has been a matter of debate. The initial protocol of prolonged intravenous antibiotic therapy for 6–8 weeks has given way to short-term intensive intravenous therapy at many centers till normalization or downtrending of laboratory markers including CRP and ESR along with clinical improvement. This is then followed by appropriate oral antibiotic therapy for up to 6 weeks on a case-to-case basis.

COMPLICATIONS AND SEQUELAE

A well-known complication of AHOM is chronic osteomyelitis. This results from bone necrosis from chronic inflammation and subsequent vascular compromise of the subperiosteal bone. It often results in sequestrum formation and is thus a constant source of infection with a resultant discharging sinus. The treatment of chronic osteomyelitis can be divided into surgical and medical. Surgery consists of debridement, sequestrectomy and antibiotic-impregnated cement bead insertion. Medical management includes prolonged antibiotic therapy. Acute
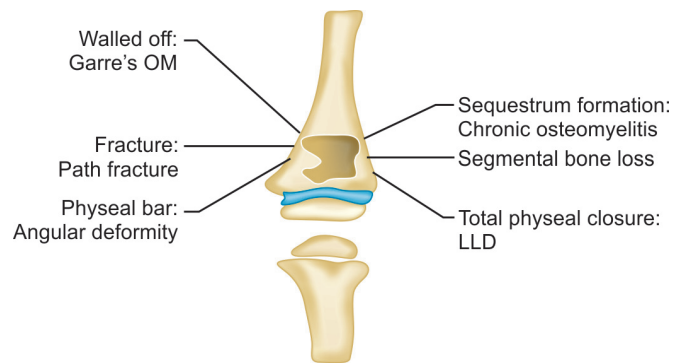
Figure 3 A schematic representation showing the various sequelae of acute osteomyelitis
Abbreviations: OM, osteomyelitis; LLD, limb-length discrepancy

osteomyelitis around the metaphyseal and physeal region can result in physeal arrest with a physeal bar formation, which can cause either limb length discrepancy or angular deformities. It is very difficult to treat and more often than not requires extensive reconstructive surgery. Pathological fractures can and do occur frequently and are exceedingly difficult to treat due to the presence of infective material in the vicinity of the fracture which makes it prone to go into nonunions **(Fig. 3)**. In the current state-of-the art complex, three-dimensional computer-assisted external ring fixators in the form of spatial frames are available for treatment and stabilization of bones being treated for chronic osteomyelitis with or without fractures or nonunion, for bone transportation including limb length restoration and for deformity correction **(Fig. 4)**.

Figure 4 Patient underwent three-dimensional (3D) complex computer-assisted Taylor spatial frame after appropriate debridement of the infection with wound vacuum-assisted closure (VAC) placement. Frame was on for 8 weeks in this case leading to successful healing and deformity correction

MORE ON THIS TOPIC

Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant *Staphylococcus aureus*. J Pediatr Orthop. 2006;26:703-8.

Copley LA. Pediatric musculoskeletal infection: trends and antibiotic recommendations. J Am Acad Orthop Surg. 2009;17:618-26.

Gutierrez K. Bone and joint infections in children. Pediatr Clin North Am. 2005;52:779-94, vi.

Jackson MA, Nelson JD. Etiology and medical management of acute suppurative bone and joint infections in pediatric patients. J Pediatr Orthop. 1982;2:313-23.

Lundy DW, Kehl DK. Increasing prevalence of *Kingella kingae* in osteoarticular infections in young children. J Pediatr Orthop. 1998;18:262-7.

Thomsen I, Creech CB. Advances in the diagnosis and management of pediatric osteomyelitis. Curr Infect Dis Rep. 2011;13:451-60.

IN A NUTSHELL

1. Osteomyelitis in combination with acute septic arthritis is a serious condition and requires emergent attention especially in children to prevent complications and often disastrous sequelae.
2. Acute hematogenous osteomyelitis is the most common type of osteomyelitis, which occurs due to the bacterial seeding of the metaphyseal region.
3. The child presents with typical pseudoparalysis with a tender, swollen limb with fever. Clinical examination and index of suspicion is critical.
4. Magnetic resonance imaging is increasingly becoming a primary modality of diagnostic investigation especially in early cases.
5. Surgical management involves drainage of the subperiosteal and intramedullary collection, curettage of the involved bone and cortical decompression in indicated cases.
6. Intravenous antibiotics are initially necessary followed by a course of oral antibiotics in many cases.
7. Common complications of AHOM include chronic osteomyelitis, pathological fractures, gap nonunions, physeal bar formation, and deformities.

Chapter 49.3
Septic Arthritis
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Septic arthritis—as the term implies is an infection of the synovial joint due to the invasion of microorganisms, most commonly pyogenic bacteria and the subsequent inflammatory response. It is one of the true orthopedic emergencies and as such requires prompt attention including likely surgical intervention and targeted medical management. Septic arthritis is unfortunately common in the developing world and the problem is sometimes magnified due to the rampant overuse of antibiotics in the intensive care unit (ICU) setting with the emergence of several resistant strains.

EPIDEMIOLOGY

The incidence of septic arthritis in infants is approximately 1 in 1,500 live births though the exact incidence is difficult to calculate due to paucity of data in literature and likely due to the fact that several cases go unreported in various parts of the world. Septic arthritis in childhood has a bimodal distribution—the first peak is during neonatal period and infancy and the second peak is between somewhere 4–8 years of age. Boys and girls are almost equally affected though with a slight male preponderance. The most common joint to be involved is the hip, followed by shoulder, knee and ankle.

ETIOLOGY

The most common organism causing septic arthritis in children is *Staphylococcus aureus* in all ages. Almost 70–90% of all osteoarticular infections (septic arthritis and osteomyelitis) in all ages occur due to *S. aureus*, though this proportion has changed slightly over the years. Most of the strains in community-acquired infections are still methicillin-sensitive *S. aureus* though infections caused by methicillin-resistant *S. aureus* (MRSA) are becoming increasingly common in the ICU setting and in hospitals.

The other common organisms are *Streptococcus pyogenes* in neonates and *Haemophilus influenzae* in older children as well as gram-negative organisms like *Pseudomonas aeruginosa*. Children who are immunosuppressed are susceptible to organisms of low virulence like *Candida* species, *Kingella kingae* and *Aspergillus*.

PATHOGENESIS

Septic arthritis usually is of hematogenous origin, but can arise through direct inoculation. It can occur from the primary seeding of the synovial membrane, secondarily from infection in the adjacent metaphyseal bone, or directly from infection in the adjoining epiphysis.

When septic arthritis occurs, bacteria rapidly invade the joint space and within no time, can cause intense inflammation along with synovial necrosis. There is formation of fibrinous exudates and release of endotoxins in some cases. This leads to synovial destruction along with release of proteolytic enzymes like proteases, peptidases and collagenases from the leukocytes which are present in large numbers. The resultant cellular breakdown and the loss of glycosoaminoglycans are the first measurable change in the articular surface which can occur as early as 8 hours after the bacteria are introduced into the joint (depending on the virulence of the organism, the bacterial load and the patient immunity). Collagen destruction soon follows and the resultant effusion and elevation of intracapsular pressure and vascular thrombosis result in articular destruction. In certain joints like hip, infection distends and softens joints capsule and may cause joint articulating issues including subluxation or dislocation.

In very young children (younger than 18 months), septic arthritis can occur due to extension of metaphyseal infection through the metaphyseal blood vessels (i.e., as an extension of metaphyseal osteomyelitis). This commonly occurs in the hip and shoulder where the proximal epiphysis is intra-articular.

The third mechanism which commonly occurs in clinical setting is the direct inoculation. This occurs especially in the newborn intensive care unit (NICU) setting where femoral puncture is done regularly and infection in the hip may occur due to possibly compromised asepsis. Hence, it is exceedingly important for the clinician caring for children in ICU settings to be extremely vigilant and careful during femoral punctures about the sterility and the commonly taught method of *advancing the needle till you hit bone and then withdraw* in femoral punctures should be reconsidered.

CLINICAL FEATURES

The clinical features of septic arthritis in children vary according to the virulence of the organism, age of the child as well as the immune status of the patient. In neonates and infants, the child presents with typical pseudoparalysis, i.e., inability or reluctance to move the affected limb along with pain **(Fig. 1)**. This may be accompanied by features of systemic toxicity including fever, irritability and tachycardia. There are usually local signs of inflammation like warmth, redness and swelling, though this may be masked in deeper joints like the hip and in immunocompromised patients.

In children, who are immunosuppressed due to any cause, or in NICU graduates and have been subjected to long-term higher antibiotics, the classical signs of systemic toxicity may be masked. However, pseudoparalysis is a fairly consistent sign even in these children.

In older infants and children, septic arthritis in the lower limb especially the hip, presents with classical features of inability to bear weight on that limb along with other features similar to those described above. In the diagnosis of septic arthritis of the hip, the *Kocher's criteria* can be helpful. The Kocher's criteria (described by Mininder Kocher et al. in 1999) are fever (> 38°C), inability to bear weight, white blood cell (WBC) count greater than 12,000/mm³ and erythrocyte sedimentation rate (ESR) greater than 40 mm/hour. The sensitivity is almost 99% if all four criteria are present. Children's Hospital of Philadelphia added the fifth criteria in the form of C-reactive protein (CRP).

INVESTIGATIONS

Plain radiographs The role of plain radiographs in the diagnosis of septic arthritis is minimal, especially in the early stages. Plain

Figure 1 Clinical intraoperative photograph of a 4-year-old child with septic arthritis of the right knee. Photograph shows purulent fluid being aspirated from the knee joint using a thick bore needle

radiographs may be useful in order to rule out concomitant osteomyelitis in the slightly delayed presentations. They are also useful in the diagnosis and classification of sequelae of septic arthritis, especially septic arthritis of the hip.

Ultrasonography (USG) It is very useful to detect any joint effusion. Although USG cannot clearly differentiate between pus and synovial fluid, in experienced hands USG-guided aspiration may be very useful to confirm the diagnosis. However, USG has limitations—it is fairly operator-dependent and is especially difficult in small infants and neonates and requires very small probes for accuracy. It is also very difficult to perform the ultrasound in an acutely tender joint since the probe pressure can cause severe discomfort to the patient. The newer modality of power Doppler USG has been found to be of great use especially in the early diagnosis of vascular complications of septic arthritis and the resultant tamponade due to synovial effusion.

Bone scan Bone scans are both sensitive and specific. Bone scan can detect abnormalities within 2–3 days of onset of symptoms. The main disadvantage of bone scan is the very high amount of radiation exposure.

Magnetic resonance imaging (MRI) It is emerging as the gold standard in the diagnosis of septic arthritis especially in those where it is feasible to obtain. MRI is more sensitive than ultrasound in the detection of effusion and also helps in the diagnosis of any bony changes and osteomyelitis. It can also differentiate between septic arthritis, inflammatory arthritis and transient synovitis on the basis of marrow edema and amount of synovial thickening. MRI helps in deciding the timing of surgeries as well as planning the surgical approach. The main disadvantage of MRI in the pediatric setup is the requirement of general anesthesia in some kids.

Hematological investigations Complete blood count (CBC) with differential count and ESR are very useful in the management. CRP estimation is a helpful parameter which is highly sensitive for infection. It is also indicative of the response of treatment and therapy and a downtrending and normalizing CRP is helpful in deciding the course of antibiotic care and changing route of administration.

Blood culture is highly recommended and sometimes it can identify the pathogen. However, the blood sample must be promptly analyzed after collection and any contamination must be prevented. Organism identification is extremely important for both, confirmation of the diagnosis and guiding antimicrobial selection. Needle aspiration is likely to grow an organism in almost 50–60% of cases whereas blood cultures can yield positive results in one-third to little more than half of specimens.

DIFFERENTIAL DIAGNOSIS

In neonates and very young infants, the differential diagnosis for septic arthritis is any cause of *pseudoparalysis*, namely physeal injuries, scurvy and hemarthrosis due to any cause. In older children, the main differential diagnosis is transient synovitis as well as other causes of painful antalgic gait like osteoarticular tuberculosis, acute slipped capital femoral epiphysis and hemarthrosis in bleeding dyscrasias.

MANAGEMENT

Treatment consists of balance between surgical and medical measures. The pus and granulation tissue has to be evacuated surgically along with medical management of sepsis by appropriate antibiotics and anti-inflammatory agents.

Joint Management

Emergent surgical decompression with drainage and irrigation of the joint is of paramount importance for the effective management of acute septic arthritis. Usually, open surgical drainage is advised especially in deeper joints like hip and shoulder. In some superficial joints like knee or elbow, a joint aspiration and lavage can be effective **(Fig. 1)**. This modality can also be used when patient has a very high risk for anesthesia or is so sick that it is difficult to move the patient from the ICU setting.

Drainage of pus helps with decompression and also potentially improves the vascularity by removing the tamponade-like effect inside the joint **(Figs 1 to 3)**. The antibiotics which were not able to reach the infection site are now able to do so after decompression. This ultimately aids the process of healing of bone and joint due to clearance of tissue-destroying fluid and also due to decrease in the tamponade effect on the delicate circulation around the growth plate.

Pus or fluid obtained during surgery is analyzed with Gram staining and appropriate culture, which helps in selection of proper antibiotics. It is advisable to withhold antibiotics prior to drainage and sending for culture sensitivity since that can affect the final culture and sensitivity pattern unless in extremely sick and unstable patients.
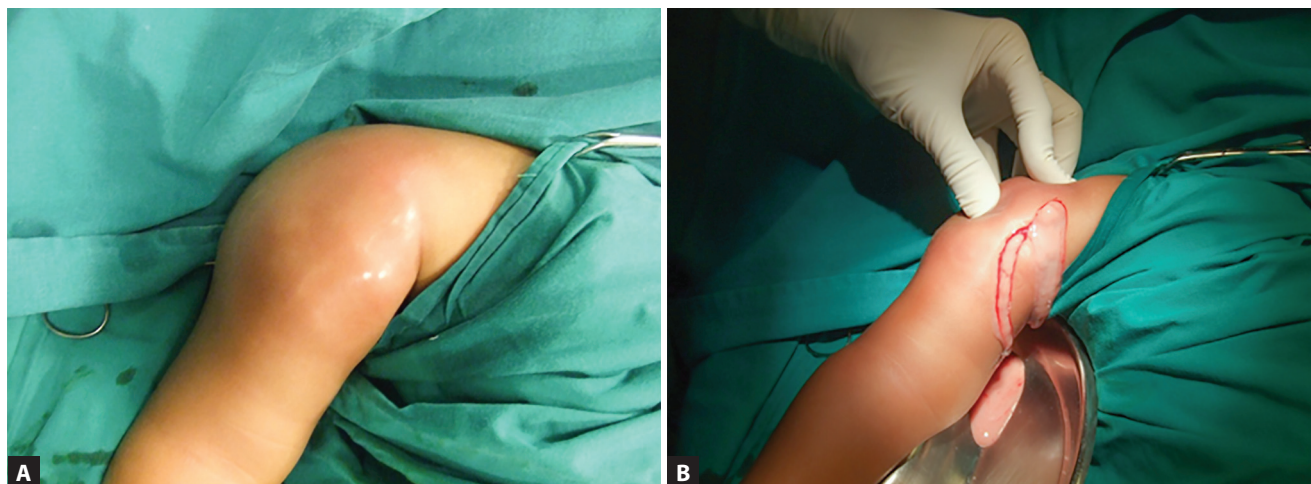
Figures 2A and B (A) Clinical photograph of a 6-year-old boy with severe swelling and redness of the right shoulder diagnosed to have septic arthritis of the shoulder. (B) Intraoperative photograph of the same child during an arthrotomy showing thick purulent fluid being drained
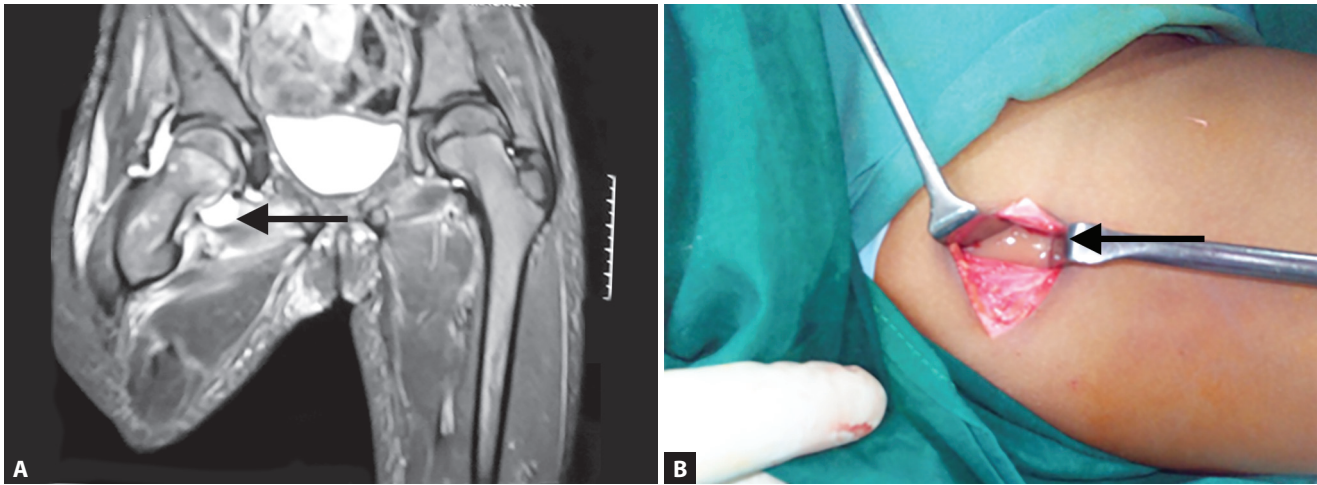
Figures 3A and B (A) T2-weighted image of the MRI of an 8-year-old girl showing fluid (pus) collection (arrow) in the right hip joint suggestive of septic arthritis of the hip. (B) Clinical intraoperative photograph of the same child during arthrotomy. Note the thick purulent fluid (pus) (arrow) seen in the wound after the capsulotomy

Medical Management

Antimicrobial therapy should start immediately after drainage of pus and infection. Antimicrobial therapy is guided by Gram stain on the aspirated pus. Initially broad-spectrum antibiotics like first-generation cephalosporins, ampicillin-cloxacillin or amoxicillin-clavulanic acid in community-acquired infections and vancomycin for hospital-acquired infections, should be started till culture/sensitivity results are obtained and then appropriate antibiotics can be started according to sensitivity report.

The initial protocol was to administer intravenous antibiotics for about 6 weeks. Recent studies have shown that short course of intravenous antibiotics followed by oral antibiotics may prove to be equally effective. In the new protocol, intravenous antibiotics are given for about 4–5 days while monitoring the CBC, ESR and CRP. Once the CRP has normalized and the ESR shows a downtrending, patient may be transitioned to oral antibiotics with infectious disease consultation and approval. Oral antibiotic therapy is continued for about 6 weeks. The main exceptions to this short-course antibiotic treatment are: immunosuppression due to any cause, a virulent organism like MRSA or *Pseudomonas* or in patients in whom culture sensitivity shows poor sensitivity for oral antibiotics.

Close monitoring of the clinical, hematological and radiological parameters is required to ensure that the treatment is effective and the outcome satisfactory. Antibiotics may be stopped by 6 weeks if the parameters improve including clinical, laboratory and imaging—with consultation from infectious disease specialist. Radiographs must be taken at intervals (about 6 months) to see for any sequelae that may develop in future.

COMPLICATIONS

Early complications include sepsis, septic shock, and pulmonary septic emboli. The common *local complications* include concomitant osteomyelitis, especially in joints like hip and shoulder, which have the physis which are intra-articular, and soft tissue abscesses which can occur due to local contiguous spread into the tissue planes in severe collections. *Late complications* include variety of deformities such as coxa vara, coxa breva, femoral neck pseudoarthrosis, coxa magna, and septic dislocations.

MORE ON THIS TOPIC

Copley LA. Pediatric musculoskeletal infection: trends and antibiotic recommendations. J Am Acad Orthop Surg. 2009;17:618-26.

Narang A, Mukhopadhyay K, Kumar P, Bhakoo ON. Bone and joint infection in neonates. Indian J Pediatr. 1988;65:461-4.

Pääkkönen M, Kallio MJ, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. Clin Orthop Relat Res. 2010;468:861-6.

Rutz E, Brunner R. Septic arthritis of the hip—current concepts. Hip Int. 2009;19 Suppl 6:S9-12.

Sultan J, Hughes PJ. Septic arthritis or transient synovitis of the hip in children: the value of clinical prediction algorithms. J Bone Joint Surg Br. 2010;92:1289-93.

Syriopoulou VP, Smith AL. Osteomyelitis and septic arthritis. In: Feigin RD, Cherry JD. Textbook of Pediatric Infectious Diseases. 2nd ed. Philadelphia: WB Saunders; 1987. pp. 759-79.

IN A NUTSHELL

1. *Septic arthritis*—as the term implies is an infection of the synovial joint due to the invasion of microorganisms, most commonly pyogenic bacteria and the subsequent inflammatory response.
2. The most common causative organism is *S. aureus* methicillin-sensitive in the community-acquired setting and methicillin-resistant (MRSA) in the hospital-acquired setting.
3. The patient presents with the typical pseudoparalysis of the limb with extreme reluctance to use that limb. In older kids, septic arthritis (especially of the hip) can be diagnosed using the Kocher's criteria, which include fever, inability to bear weight, raised ESR and raised WBC count. CRP is helpful parameter as well.
4. Magnetic resonance imaging is increasingly becoming the diagnostic modality of choice when feasible.
5. The treatment of established septic arthritis is both medical and surgical and includes decompression with drainage, debridement, and appropriate antibiotics.
6. Current approach remains either a full course of intravenous antibiotics or a protocol with initial short course of intravenous antibiotics for about 4–5 days after surgery till normalization or downtrending of CRP and improvement in clinical signs after which oral antibiotics according to culture sensitivity should be given for about 6 weeks.
7. Patient should have appropriate follow-up care, including timely imaging as needed to evaluate sequelae of septic arthritis in a timely manner.

Chapter 49.4
Neck Problems
Vijay HD Kamath, Harish S Hosalkar

Common pediatric cervical spine problems include congenital anomalies, growth and developmental disorders and acquired conditions including postural adjustments to underlying disorders. Knowledge of the normal embryology, growth, and development of the pediatric cervical spine is necessary to understand, identify and treat these conditions.

TORTICOLLIS

Torticollis is a combined rotatory and head tilt deformity and usually indicates a problem at C1–2 (because 50% of the cervical spine rotation occurs at this joint). A head tilt alone points towards a more generalized problem in the cervical spine. Congenital muscular torticollis (CMT) is the most common cause of torticollis; however, a variety of other conditions that result in torticollis, need to be rule out, especially in patients who lack the characteristic features of CMT. The etiology of torticollis may be classified as congenital and acquired **(Box 1)** or as osseous and nonosseous.

BOX 1 Differential diagnosis of torticollis

Congenital
• Congenital bone anomalies
  – Occipitovertebral junction anomalies—unilateral occipitocervical synostosis, basilar impression, odontoid anomalies
  – Cervical hemivertebra, Klippel-Feil syndrome
• Congenital soft tissue anomalies
  – Unilateral absence of sternocleidomastoid, pterygium colli

Acquired
• Congenital (infantile) muscular torticollis
• Cervical instability (atlanto-occipital subluxation, atlantoaxial subluxation, subaxial subluxation)
• Infection
  – Extraspinal—lymphadenitis, retropharyngeal abscess, tonsillitis
  – Spinal—spondylodiscitis
• Trauma
  – Muscular injury, fractures in spine, clavicle fracture, brachial plexopathy
• Inflammatory
  – Juvenile rheumatoid arthritis
• Neurogenic
  – Posterior fossa tumors
  – Intraspinal tumors
  – Dystonia (benign paroxysmal torticollis)
  – Spasmus nutans (nystagmus, head bobbing, head tilting)
  – Dystonic drug reactions (phenothiazines, haloperidol, metoclopramide)
  – Chiari type I malformation and/or syringomyelia
  – Wilson disease
• Ocular dysfunction
  – Nystagmus
  – Superior oblique paresis
• Tumors
  – Bone tumors (eosinophilic granuloma)
  – Soft tissue tumors
• Others
  – Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
  – Hysteria
  – Benign paroxysmal torticollis of infancy
  – Acute cervical disc calcification

Congenital Muscular (Infantile) Torticollis

Congenital muscular torticollis or congenital wryneck is the most common cause of torticollis in the infant and young child, presenting at a median age of 2 months and occurs in up to 1/250 live births. Involvement of the sternocleidomastoid muscle (SCM) with varying degrees of tightness or contracture results in a head tilt towards the involved side and the chin rotation towards the opposite shoulder purely based on the muscle action.

Etiology
The exact etiology is not known and there are several theories. One theory is that of SCM ischemia and an intramuscular compartment syndrome from a distorted position in utero (breech presentation) or injury occurring at the time of delivery. Another theory is differentiation and degeneration of mesenchymal cells remaining in the SCM from fetal embryogenesis. The sternomastoid muscle on one side is fibrous and fails to elongate as the child grows; consequently, progressive deformity develops.

Clinical Features
The clinical features of CMT depend on the age of the child and the severity of muscular involvement and duration of problem. In the first 4–6 weeks of life, one may identify a well-defined nontender lump located within the SCM belly. At this stage, there is neither deformity nor obvious limitation of movement and within 4–6 months the lump may gradually regress. After 4–6 months of life, contracture and torticollis are the main clinical findings. In some cases, the deformity may not become apparent until the child is 1 or 2 years of age. The head is tilted to one side, and the sternomastoid on that side may feel tight and hard. Asymmetrical development of the face with plagiocephaly (facial flattening) may be observed on the side of the contracted muscle. These features become increasingly obvious as the child grows. CMT may occur with other abnormalities that may be a consequence of intrauterine mechanical deformation including deformities of the head (plagiocephaly), face, hip [developmental dysplasia of the hip (DDH)], or foot (metatarsus adductus).

Differential Diagnosis
If the typical clinical features of CMT are absent or if there is no response to the routine treatment, other causes of wryneck **(Box 1)** should be excluded. The algorithm in **Flow chart 1** is helpful.

Treatment
If the diagnosis is made during infancy, daily muscle stretching should be encouraged and may prevent the incipient deformity. The ear opposite the contracted muscle is approximated to the ipsilateral shoulder, and the chin positioned to touch the shoulder on the same side as the contracted muscle. Nonoperative modalities are successful in most cases. Administration of botulinum toxin A (Botox®) intramuscularly into the SCM has been used in rare and resistant cases of CMT, although we would express caution about its usage by common practitioners due to inadvertent complications. If the condition persists beyond 1 year, surgery may be required to correct the wryneck and avoid progressive facial deformity. The optimal timing for surgery is debatable. However, it is generally accepted that a good window for surgical release is between the ages of 1 year and 4 years, with predictable results reported in cases operated before the age of 3 years. Older children are also known to do well with surgical release when indicated.

Other Causes of Torticollis
When the typical findings associated with CMT are absent or the usual clinical response to treatment is not observed, other causes

Flow chart 1 Algorithm for evaluation of torticollis
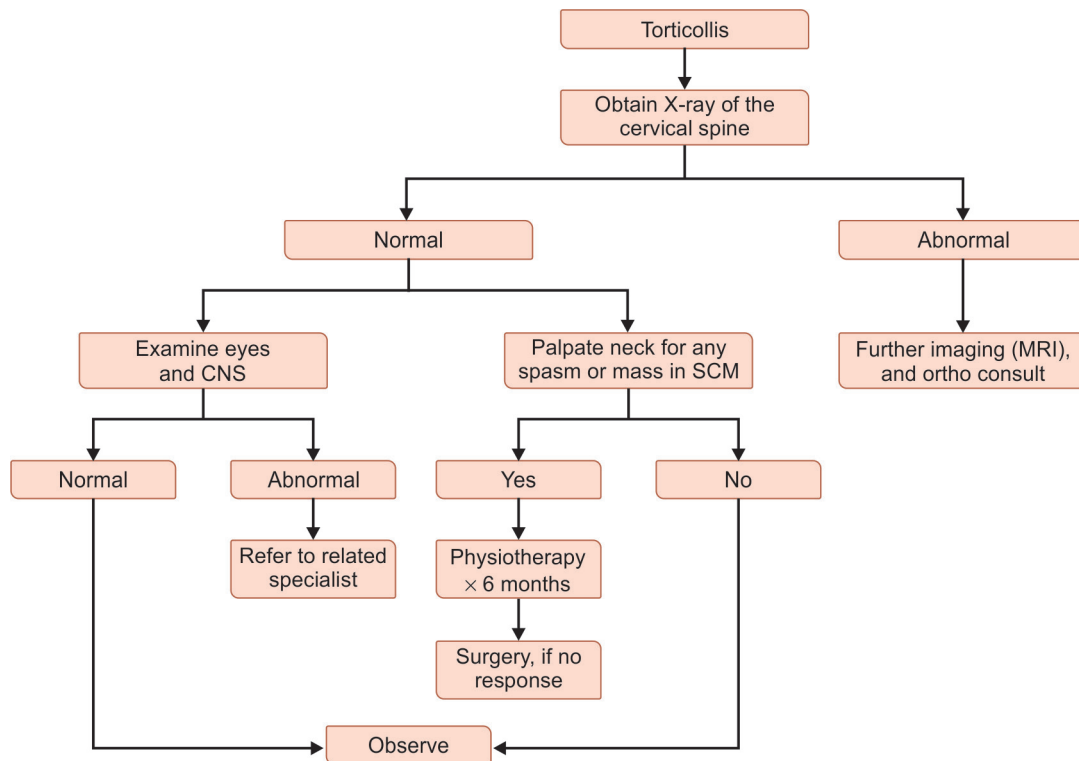
(Adapted from: Do TT. Congenital muscular torticollis: current concepts and review of treatment. Curr Opin Pediatr. 2006;18:26-9.)
Abbreviations: MRI, magnetic resonance imaging; SCM, sternocleidomastoid muscle.

of wryneck should be ruled out. A detailed clinical evaluation, additional imaging studies (plain radiographs and computed tomography (CT) scan to evaluate osseous abnormality and magnetic resonance imaging (MRI) to evaluate neural elements) and consultation with other specialists including a neurologist and ophthalmologist is often required.

Atlantoaxial Rotatory Displacement

Rotational malalignment of the atlas on the axis can vary from subluxation to a frank dislocation and the entire spectrum is termed atlantoaxial rotatory displacement. The patient presents with a wryneck and the position of the head is typically described as *cock robin position*. The SCM on the long side is often in spasm in an attempt to correct the deformity. This is unlike in CMT in which the SCM contracture causes the torticollis **(Fig. 1)**. A majority of malalignments are reducible in the initial stages, if left untreated, capsular contracture and bony adaptive changes make the deformity fixed and irreducible. Thus, prompt diagnosis and treatment is important.

A variety of conditions can lead to rotatory displacement, including minor trauma (in the spine or extraspinal, e.g., clavicle fractures, brachial plexus injury), after head and neck surgery, central line insertion, infection or inflammation in the upper airway, pharynx or neck (*Grisel syndrome*).

Routine plain radiographs including an open-mouth odontoid view are required. On the open-mouth view, the lateral mass that is rotated forward appears wider and closer to the midline, and the opposite lateral mass appears narrower and further away from the midline. Axial CT scan sections obtained with the head in neutral, maximal right and left rotation will demonstrate the amount of movement at the atlantoaxial joint and reducibility or not.

Treatment of atlantoaxial rotatory displacement is based on the underlying etiology and duration of symptoms. Patients seen within a few days of the onset of symptoms may be managed with analgesics and a soft collar. For patients with symptoms lasting greater than 1 week but less than 1 month, head halter cervical traction is applied to correct the deformity and the neck immobilized in a cervical collar for 4–6 weeks. Patients with a fixed deformity or with recurrent displacement may require an atlantoaxial fusion.

CERVICAL ANOMALIES AND INSTABILITIES

Cervical spine anomalies may occur in isolation or as part of a genetic syndrome or skeletal dysplasias. Many of these anomalies are asymptomatic and hence undiagnosed and often picked up as incidental findings or due to trauma. There appears to be no difference in clinical features or management between syndromic and nonsyndromic anomalies. Cervical instability may occur in the presence of a congenital anomaly, excessive ligament laxity (connective tissue disorders), metabolic diseases, infections and inflammatory conditions. The host of cervical anomalies and instabilities are enumerated in **Box 2**.

Basilar Impression

In this condition, the floor of the skull is indented by the upper cervical spine. The tip of the dens is more cephalad and sometimes protrudes into the opening of the foramen magnum. This may encroach on the brain stem, risking neurologic damage from direct injury, vascular compromise, or alterations in cerebrospinal fluid flow. Basilar impression can be primary or secondary and the common causes are listed in **Table 1**. *Primary basilar impression* is
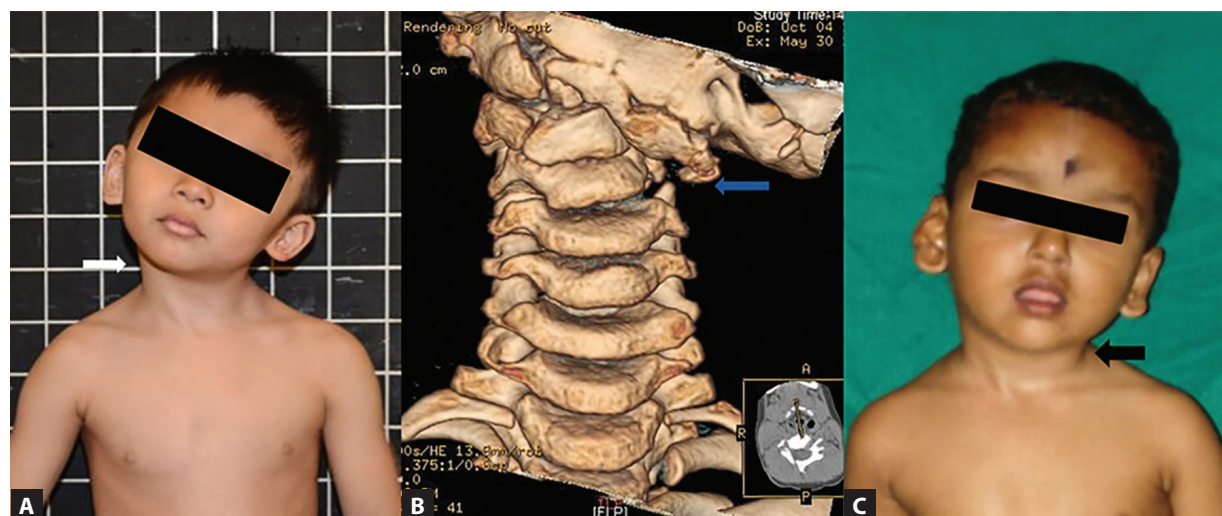
Figures 1A to C (A) 4 years child with a typical 'cock robin' position, note the sternocleidomastoid spasm (white arrow) on the patient's right–long side, (B) his computed tomography scan showed an upper cervical (blue arrow) vertebral anomaly, (C) 2 years child with a congenital muscular torticollis, note the swelling in the left sternocleidomastoid belly – short side (black arrow)
Source: Prof. Keith Luk, Hong Kong University and Dr. Vasuki, Bangalore Baptist Hospital, Bengaluru.

BOX 2 Causes of cervical instability in children and adolescents
Congenital
• Vertebral (bony anomalies)
– Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas)
– Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process)
– Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis)
• Ligamentous or combined anomalies
• Syndromic disorders
– Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Marfan syndrome, Ehlers-Danlos syndrome
Acquired
• Trauma
• Inflammatory conditions (juvenile rheumatoid arthritis)
• Infection (pyogenic, granulomatous)
• Osteochondrodysplasias (achondroplasia, spondyloepiphyseal dysplasia)
• Storage disorders (mucopolysaccharidoses)
• Metabolic disorders (rickets)
• Tumor
• Miscellaneous (including osteogenesis imperfecta, neurofibromatosis sequela of surgery)

Table 1 Common causes of basilar impression

Primary	Secondary
• Odontoid abnormalities	• Osteomalacia
• Morquio syndrome	• Rickets
• Klippel-Feil syndrome	• Rheumatoid arthritis
• Atlas hypoplasia	• Neurofibromatosis
• Atlanto-occipital fusion	• Renal osteodystrophy
	• Bone dysplasias

a congenital structural abnormality of the craniocervical junction that often is associated with other vertebral defects. *Secondary basilar impression* is a developmental condition attributed to softening of the osseous structures at the base of the skull. Softening allows the odontoid to migrate cephalad and into the foramen magnum.

Clinical Features

These patients typically have short necks. This shortening is only an apparent deformity because of the basilar impression. Asymmetry of the skull and face (68%), painful cervical motion (53%), and torticollis (15%) can also occur. Neurologic symptoms and signs are often present and can occur. Symptoms are of raised intracranial pressure (because the aqueduct of Sylvius becomes blocked) and or myelopathy (because of direct compression or ischemia of the cord).

Diagnosis

The relationship between the odontoid process and the foramen magnum can be determined on radiographs; the most commonly used lines are Chamberlain's, McRae's, and McGregor's **(Fig. 2)**. McGregor's line is the best line for screening because the
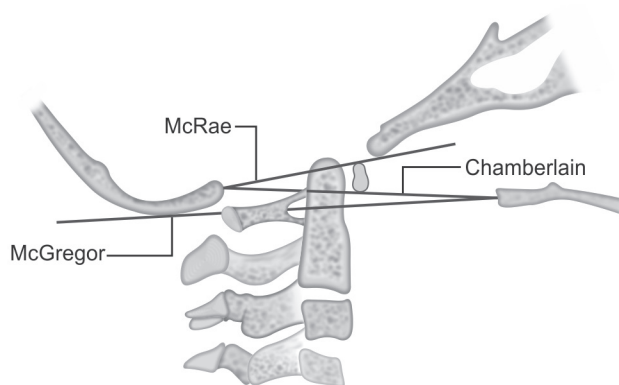
Figure 2 Lines for assessing basilar invagination on a lateral radiograph of the craniocervical junction. The McRae's line (basion to opisthion), demonstrates the amount of odontoid protrusion into the foramen magnum, is abnormal whenever the odontoid tip protrudes beyond and into the foramen magnum. Chamberlain's line is drawn from the posterior lip of the foramen magnum to the dorsal margin of the hard palate. The odontoid bisects this line in early basilar invagination. The McGregor's line runs from the upper surface of the posterior edge of the hard palate to the most caudal point of the skull (> 4.5 mm is abnormal)

landmarks can be clearly defined at all ages on a routine lateral radiograph. Further information is obtained with CT or MRI.

Treatment

Patients with basilar impression and no neurological symptoms or with minimal symptoms and no sign of progressive neurological damage should be observed and examined periodically. Treatment of patients with neurological deficits involves surgical decompression and stabilization.

Odontoid Anomalies

Congenital anomalies of the odontoid though rare are of importance as they can result in atlantoaxial instability. Congenital anomalies of the odontoid may be classified as aplasia, hypoplasia, and os odontoideum **(Figs 3A to D)**. A complete absence of the odontoid is termed *aplasia*. Partial development of the odontoid as hypoplasia; the bone size varies from a small, peg-like projection to almost normal size. In *os odontoideum,* the odontoid is a separate ossicle with a smooth, sclerotic border, which is separated from the axis by a transverse gap, leaving the apical segment without its basilar support.

Diagnosis

These anomalies usually are detected as incidental findings in a routine cervical spine radiograph following trauma or when symptoms occur due to atlanto-occipital instability. Patients may present with pain or torticollis, or neurological compressive symptoms such as transient paralysis, myelopathy or sphincter disturbances. Atlantoaxial instability may compress the vertebral artery resulting in cervical and brain stem ischemia, presenting as vertigo, visual disturbances, syncope or seizures. Absence of involvement of cranial nerves is an important clue to differentiate os odontoideum from other occipitovertebral anomalies because the spinal cord impingement occurs below the foramen magnum.

The anomaly should be suspected (and looked for even if the child does not complain) in skeletal dysplasias which involve the spine such as Down syndrome, Klippel-Feil syndrome (KFS), Morquio syndrome, and spondyloepiphyseal dysplasia. This is especially important in patients undergoing surgery as the atlantoaxial joint may subluxate under anesthesia.

Odontoid anomalies can be diagnosed on routine lateral view and open-mouth odontoid view radiographs. CT scans are useful in further delineating the bony anatomy, and flexion and extension lateral radiographs help in assessing instability.

Management

The concern in congenital odontoid anomalies is that even minor trauma can sometimes result in atlantoaxial joint subluxation or dislocation causing permanent neurological damage or death. This raises the controversy of whether prophylactic surgical treatment of asymptomatic patients should be routinely performed or not. These patients are strongly advised against playing contact sports. Patients with pain or torticollis usually improve with cervical traction or immobilization. Atlantoaxial fusion is indicated if there is (1) neurological involvement, (2) anterior or posterior instability of more than 5 mm, (3) asymptomatic patients with an instability index greater than 40% and/or a sagittal plane rotation angle more than 20°, and (4) persistent neck complaints associated with atlantoaxial instability, not relieved by conservative treatment.

KLIPPEL-FEIL SYNDROME (CERVICAL VERTEBRAL SYNOSTOSIS)

Klippel-Feil syndrome (KFS) is a congenital fusion of the cervical vertebrae that may involve two segments, a congenital block vertebra, or the entire cervical spine. It is often associated with other musculoskeletal and system anomalies. Vertebral fusion results from a failure of segmentation of the cervical somites during the 3rd to 8th weeks of life. The embryologic insult, although yet unknown, is not limited to the cervical vertebrae, explaining the other associated anomalies with KFS. Among the proposed etiologies for KFS are (1) a primary vascular disruption during embryonic development; (2) maternal alcoholism (high incidence in fetal alcohol syndrome); and (3) inherited autosomal dominant.

Clinical Features

The classic triad of KFS is low posterior hairline, short neck, and limited neck motion; however, fewer than half of patients with KFS have all features. Many patients with KFS have a normal
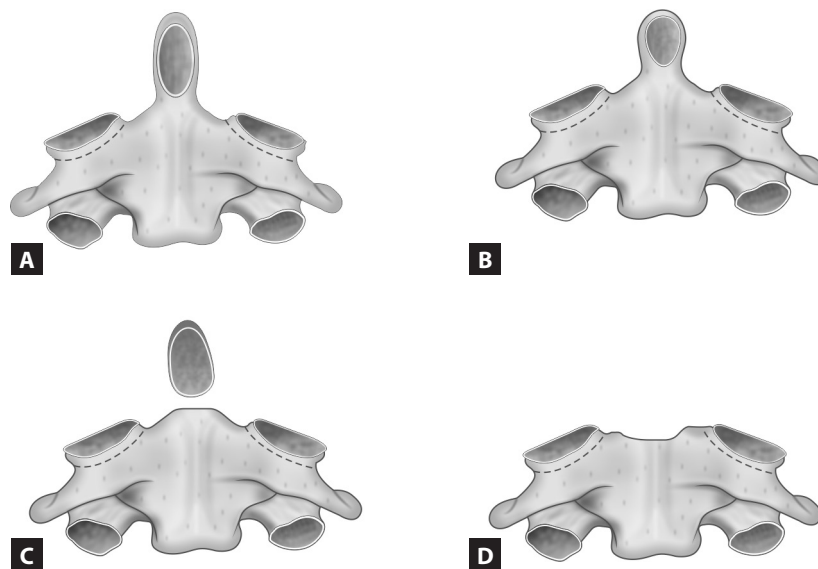
Figures 3A to D Types of odontoid anomalies. (A) Normal odontoid; (B) Hypoplastic odontoid; (C) Os odontoideum; (D) Aplasia of odontoid

appearance, and the syndrome is diagnosed through incidental radiographs. The most constant feature is limitation of neck motion; the extent of limitation depends on the extent of the anomaly. Symptoms tend to arise in the second or third decades, not from the fused segments but from the hypermobile adjacent segments. There may be pain due to segmental hypermobility or neurological symptoms from instability.

Associated Anomalies

Approximately one-third of patients have an associated Sprengel's deformity **(Fig. 4A)**. The other anomalies associated with the syndrome are scoliosis (60%, either congenital or idiopathic), cervical ribs (12–15%), congenital limb deficiency, hand deformities (syndactyly, thumb hypoplasia and extra digits), genitourinary anomalies, deafness (30%), synkinesis (mirror movements in 20%), pulmonary dysfunction, and congenital heart disease. Goldenhar syndrome, Mohr syndrome, and fetal alcohol syndrome are also associated with congenital fusion or anomalies of the cervical spine.

Diagnosis

Routine anteroposterior (AP) and lateral X-rays reveal varying degrees of vertebral fusion, ranging from simple block vertebrae to multiple and bizarre anomalies **(Figs 4B, C)**. Feil classified the syndrome into three types depending on the extent of vertebral involvement: (1) *type I* involves the cervical and upper thoracic vertebrae, (2) *type II* involves the cervical vertebra alone, and (3) *type III* involves the cervical vertebra as well as lower thoracic or upper lumbar vertebrae. A common pattern is fusion of C1–2 and C3–4, leading to a high risk of instability at the unfused C2–3 level. Flexion and extension lateral radiographs are useful to assess for cervical instability. An MRI is recommended whenever there is any concern for neurologic involvement on clinical exam, as well as before any orthopedic spinal procedure.

A thorough evaluation should be undertaken to ensure that no congenital renal (ultrasound for initial evaluation), cardiac (ECHO) exist. Flexion-extension lateral radiographs should also be obtained before any general anesthetic to rule out any occult instability of the cervical spine.

Management and Prognosis

The natural history of these children primarily depends on the occurrence of severe renal or cardiac problems, which may limit life expectancy. Instability of the cervical spine can develop with neurologic involvement, especially in the upper segments or in those with iniencephaly. Later in life, degenerative joint and disc disease may develop in those with lower segment instabilities. Because children with large fusion areas are at high risk for developing instabilities, contact sports may be avoided. Mechanical symptoms caused by the hypermobile segment usually respond to traction, a cervical collar, and analgesics. Neurological symptoms usually require surgical stabilization with or without decompression depending on the compressive etiology. The real dilemma is whether prophylactic stabilization should be undertaken for asymptomatic hypermobile segments. To date, there are no guidelines on this topic. Surgery solely for cosmesis is unwarranted and certainly fraught with risks and complications.

CERVICAL SPINE INFECTIONS

Pyogenic Infection

Pyogenic infection of the cervical spine is uncommon, and often missed in the initial stages. It affects all pediatric age ranges, and is more common in boys than in girls. The organism, usually *Staphylococcus* spreads hematogenously and most often localizes in the adjacent vertebral end plates of a disc space. Bony destruction first occurs at the end plates and then spreads to the rest of the vertebral body. End plate involvement results in loss of nutrition to the intervertebral disc with resulting necrosis. Abscess formation occurs and pus may spread into the spinal canal or along the soft tissue planes of the neck.

Clinical Features

The child presents with acute onset neck pain and stiffness, fever and malaise. A history of preceding otitis media, urinary tract infections, or pulmonary infections is common. Neck movements are severely restricted. Blood tests may show a leukocytosis and an increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Blood culture may be positive in febrile states.
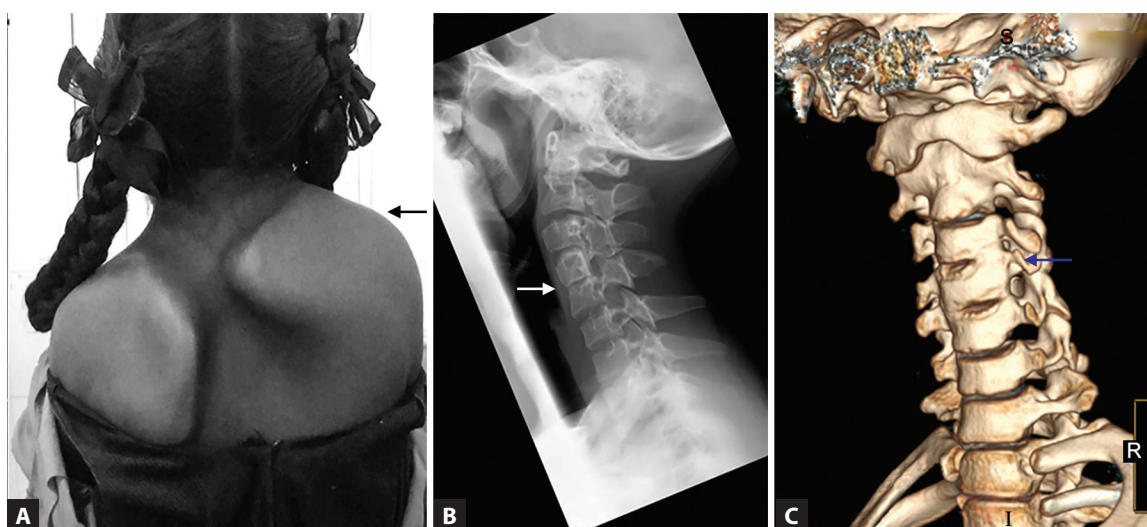
Figures 4A to C Klippel-Feil syndrome (A) 6-years-old child with Klippel-Feil syndrome and an associated Sprengel deformity (black arrow), (B) radiograph and (C) corresponding computed tomography scan showing congenital fusion of C3,4,5 vertebra (white, blue arrow)
Source: Prof. Keith Luk, Hong Kong University and Dr. Vasuki, Bangalore Baptist Hospital, Bengaluru.

Radiographs at first may not demonstrate any abnormality or loss of disc space height; later on, there may be end-plate irregularities, increased prevertebral soft tissue shadow and obvious signs of bone destruction. The MRI findings are consistent with spondylodiscitis. Bone scans are very useful in identifying the presence of discitis and osteomyelitis in a child with systemic symptoms when the anatomic location cannot be localized on clinical examination.

Management

Empiric antibiotics for *Staphylococcus aureus* are successful in most of the cases. The duration of antibiotics is debatable; however, a combined 1- to 2-week parenteral administration followed by 4–6 weeks of an oral regime is considered adequate. The cervical spine is *immobilized* by traction; once the acute phase subsides, a collar may suffice. Systemically ill patients with documented abscesses or an evolving neurological deficit may need surgery. CRP and ESR are helpful in monitoring the treatment.

Tuberculosis

Cervical spine tuberculosis (TB) is rare compared with other levels of the spine. TB of the craniovertebral junction accounts for 0.3–1% of all cases of spinal TB. Hematogenous spread of the organism from a primary focus localizes in the adjacent end plates of the disc (paradiscal type) or in the vertebral bodies (central type). With bone necrosis and destruction, the cervical spine collapses into kyphosis. A prevertebral abscess may form and present as; a retropharyngeal abscess, point behind the sternomastoid muscle or even track along the nerve to present in the axilla. An intraspinal abscess/necrotic bone may compress the spinal cord resulting in neurological signs varying from mild weakness to tetraplegia.

Clinical Features

With upper cervical spine involvement, the children present with neck pain and stiffness; torticollis, headaches, and constitutional symptoms may also be present. In cases of lower cervical spine involvement, the children may present with the same symptoms, and in addition may have dysphagia, asphyxia, inspiratory stridor and kyphosis. Neurologic symptoms vary from none to the extreme involving severe quadriparesis. On examination, the neck is tender with restriction of all movements due to pain. In late presentations, there may be cervical kyphosis, a retropharyngeal swelling or a fluctuant abscess in the posterior triangle of the neck.

Investigations

Radiographs show narrowing of the disc space, vertebral end plate erosion and increased width of the retropharyngeal soft tissue space in the early stages with vertebral collapse and kyphosis in the later stages.

Blood tests may show an increased ESR. Needle biopsy should be performed to confirm diagnosis: tissue should be sent for histopathology [granulomas with Langhans giant cells ± acid-fast bacilli (AFB)] and MTB culture and sensitivity test [Löwenstein-Jensen (LJ) medium or Bactec radiometric system or Mycobacteria Growth Indicator Tube (MGIT)]. Automated nucleic acid amplification tests for detecting *Mycobacterium tuberculosis* DNA as well as rifampicin resistance (Xpert MTB/RIF) may be used for rapid diagnosis. In view of the rising incidence of MDR and XDR TB assessing for resistance is becoming increasingly important.

Treatment

Anti-TB chemotherapy drugs are the mainstay of treatment. In the initial stages, *immobilization* of the neck in a cervical hard collar or a halo vest is required. Surgery is indicated to drain a retropharyngeal abscess if causing respiratory embarrassment; in the presence of neurological deficits; or to fuse an unstable spine.

CERVICAL SPINE IN DOWN SYNDROME

Because of underlying collagen defects and ligamentous hyperlaxity in children with Down syndrome, cervical instabilities can develop at both the occiput-C1 (up to 60% of children) and C1–C2 (40% of children) levels. Involvement of the subaxial spine is less common in children and more often observed in adults patients with Down syndrome.

Most children with atlantoaxial or occipitoatlantal hypermobility are asymptomatic. When symptoms occur, they are usually pyramidal tract symptoms, such as gait abnormalities (increased tripping or falling, may be the earliest sign), decreased exercise tolerance, and quadriparesis. Occasionally, local symptoms exist such as head tilt, torticollis, neck pain, and limited neck mobility. Rarely does sudden catastrophic death occur. Although detailed neurologic examination may be difficult; however, subtle signs such as clonus and hyperreflexia may be identified early.

Lateral neutral, flexion and extension radiographs can be used for the diagnosis and monitoring of children with hypermobility or instability. The stability of the atlantoaxial joint is assessed on radiographs by measuring the atlantodens interval (ADI). An ADI of less than 4.5 cm is considered normal in children with Down syndrome. An ADI between 4.5 mm and 10 mm may reflect hypermobility. These children are not considered at increased risk neurologic involvement. An ADI greater than 10 mm indicates a significant risk of neurologic insult. A dynamic MRI (performed in flexion and extension) helps to further evaluate atlantoaxial instability and in the absence of a static neural compression, determines the presence of dynamic compression. It is also useful to evaluate instability of the occipitoatlantal joint, which is difficult to assess reliably on radiographs.

There are no formal guidelines for monitoring of potential cervical instability in children with Down syndrome. All children with Down syndrome should undergo a clinical assessment and radiographs of the cervical spine (AP, lateral flexion, lateral extension). Neurologic examination should be conducted at least every year. Cervical radiographs may be obtained every alternate year if the clinical examination is normal. Those having an abnormal symptoms or clinical findings can be recommended an MRI in flexion and extension. Patients with normal radiographs and neurology may be allowed to participate in a full level of activities. Patients with hypermobility should be cautioned about contact sports and other high-risk activities that might possibly increase the risk of trauma to the cervical spine. Patients with myelopathy or instability (ADI > 10 mm) with impending neurologic deficit will require atlantoaxial (or occipitocervical) fusion.

CERVICAL SPINE IN MARFAN SYNDROME

Marfan syndrome affects ligamentous laxity and bone morphology. It is caused by a mutation in the glycoprotein fibrillin, which has been mapped to the long arm of chromosome 15. The abnormalities noted on radiographs usually are: focal cervical kyphosis involving at least three consecutive vertebrae (16% of patients), loss of normal cervical lordosis (35%), atlantoaxial hypermobility (approximately 54%) and basilar impression (36%).

In spite of the abnormalities seen in patients with Marfan syndrome, symptoms and neurologic compromise are rare. Patients with Marfan syndrome should be cautioned regarding participation in contact sports with high-impact loading on the cervical spine.

CERVICAL SPINE IN 22q11.2 DELETION SYNDROME

Deletion of chromosome 22q11.2 is the most commonly known interstitial chromosome deletion in humans, with an estimated prevalence of 1 in 4,000–6,000 live births. The syndrome encompasses a wide spectrum of abnormalities, including cardiac, palate, immunologic and orthopedic anomalies. At least one anomaly of the occiput or cervical spine is observed in all patients. Occipital anomalies observed include platybasia and basilar impression. C1 variations include dysmorphic shape, open posterior arch, and occipitalization, and axis variations include a dysmorphic dens. A range of cervical vertebral fusions has been noted in these patients. Increased segmental motion is observed on dynamic imaging in greater than 50% of patients, often at more than one level. Central nervous system anomalies such as Chiari type I malformation have also been reported. All patients should have screening radiographs, and many require follow-up for the cervical spine.

MORE ON THIS TOPIC

Cheng JC, Tang SP, Chen TM, et al. The clinical presentation and outcome of treatment of congenital muscular torticollis in infants—a study of 1,086 cases. J Pediatr Surg. 2000;35:1091-6.

Do TT. Congenital muscular torticollis: current concepts and review of treatment. Curr Opin Pediatr. 2006;18:26-9.

Drummond DS, Hosalkar HS. Treatment of cervical instability. In: Clark CR, Benzel EC, Cervical Spine Research Society Editorial Committee. The Cervical Spine. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2005. pp. 427-47.

Hensinger RN. Osseous anomalies of the craniovertebral junction. Spine (Phila Pa 1976). 1986;11:323-33.

Herman MJ. Torticollis in infants and children: common and unusual causes. Instr Course Lect. 2006;55:647-53.

Hosalkar HS, Sankar WN, Wills BP, et al. Congenital osseous anomalies of the upper cervical spine. J Bone Joint Surg Am. 2008;90:337-48.

Mehrotra A, Das KK, Nair AP, et al. Pediatric cranio-vertebral junction tuberculosis: management and outcome. Childs Nerv Syst. 2013;29:809-14.

Samartzis D, Kalluri P, Herman J, et al. 2008 Young Investigator Award: the role of congenitally fused cervical segments upon the space available for the cord and associated symptoms in Klippel-Feil patients. Spine (Phila Pa 1976). 2008;33:1442-50.

Sankar WN, Wills BP, Dormans JP, Drummond DS. Os odontoideum revisited: the case for a multifactorial etiology. Spine (Phila Pa 1976). 2006;31:979-84.

IN A NUTSHELL

1. Congenital muscular (infantile) torticollis is the most common cause of wryneck.
2. Neurological symptoms due to involvement of upper cervical spine may occur due to cord compression, vertebral artery compression, blockage of the aqueduct of Sylvius and cranial nerve compression. The structure compressed depends on the anomaly.
3. Congenital anomalies can most often be diagnosed on routine AP, lateral and open-mouth radiographs. Dynamic radiographs (flexion/extension views) are required to assess instability. MRI and CT scan help to further delineate the anomaly and assess neural compression.
4. Asymptomatic cervical instability may occur in the presence of a congenital anomaly, excessive ligament laxity (connective tissue disorder), metabolic disease, syndromic disorders (Down) and inflammatory [juvenile idiopathic arthritis (JIA)] pathologies. Children with these disorders need an assessment of cervical spine stability especially if being given general anesthesia.
5. Tuberculosis of the spine can be managed effectively with antitubercular chemotherapy and appropriate bracing in a majority of patients.

Chapter 49.5
Scoliosis and Kyphosis
Vijay HD Kamath, Harish S Hosalkar

Spinal deformity may be congenital, developmental, or post-traumatic. Spinal deformity can be a cause for cosmetic concern. Progressive spinal deformity can present with pain, neurological deficits, cardiopulmonary dysfunction and problems of gait and sitting balance [in neuromuscular scoliosis (NMS)]. Early detection certainly helps to outline treatment and control rapid progression while potentially preventing complications in the long run.

NORMAL SPINAL BALANCE

In the coronal plane, the spine is almost straight with the head centered over the pelvis. The mature spine has four balanced curves in the sagittal plane: (1) a cervical lordosis, (2) a thoracic kyphosis (measuring about 20°–50°), (3) a lumbar lordosis (measuring about 31°–79°) and (4) a kyphotic curve at the sacral level. The fetal and neonatal spines are entirely kyphotic. The lordosis begins to develop in the cervical spine when the child starts head holding. Lumbar lordosis develops when the child assumes an upright posture. These curves balance each other so that the head is centered over the pelvis. It is important to maintain the center of gravity for balance and to maintain an upright posture.

Spinal deformity in simple term could be stated as an abnormal curvature of the spine. The deformity is known as scoliosis (occurring in the coronal plane), or hyperkyphosis and hyperlordosis (in the saggital plane). It may occasionally occur as a combination (kyphoscoliosis).

SCOLIOSIS

Scoliosis, commonly described as a lateral curvature of the spine in the coronal plane, is in essence a triplanar deformity. It has lateral, anteroposterior and rotational components. A coronal plane curvature of greater than 10° (using the Cobb method) is termed as *scoliosis*, while curves less than this are generally termed *spinal asymmetry*. Scoliosis can be broadly classified as *compensatory* and *structural*.

Compensatory (Nonstructural) Scoliosis

In compensatory scoliosis, the deformity is obviously compensatory to an abnormality outside the spine, such as in the shortening of the lower limb, or abduction or adduction contracture of the hip. Both these conditions can result in a pelvic tilt that causes a lumbar curve. The convexity of this curve is away from the short leg. When the limb length asymmetry is corrected (during sitting or by placing blocks under the short limb), the curve tends to disappear. Children with limb-length inequality can also have a coexisting structural scoliosis. The diagnosis is confirmed if the curve persists on a standing radiograph obtained after correcting the limb-length discrepancy.

Structural Scoliosis

Structural scoliosis refers to a noncorrectable deformity of the affected spinal segment. The initial curve is probably correctable, but once it exceeds a certain point of mechanical stability, the spine buckles and rotates into a fixed deformity. To counterbalance the primary curve and maintain spinal balance, secondary (compensatory) curves nearly always develop. Secondary curves

are more easily correctable, but they too become fixed, with passage of time.

No etiology can be identified in most cases of structural scoliosis. These are termed *idiopathic*. Other etiologies of structural scoliosis based on associated conditions are listed in **Table 1**.

Clinical Features of Scoliosis

Spinal deformity is usually the presenting symptom as a rib hump, asymmetry in height of both shoulders **(Fig. 1A)** or breast (thoracic scoliosis), or asymmetrical positioning of hips (lumbar scoliosis). Balanced curves may not get noticed until adulthood when they can present with backache. Childhood scoliosis is usually painless; a complaint of pain should prompt a search for a neural etiology.

On general examination, look for café-au-lait spots, facial dysmorphism, ligamentous laxity and other features which would suggest a nonidiopathic etiology for scoliosis. The *single breath count* is a simple clinical measure of pulmonary function. The patient should be examined from the back, side and front. Midline cutaneous abnormalities of the back such as hemangiomas, hair patch, sacral dimple or skin tag are sought. Large curves are obvious, however, small curves can be detected only when the child bends forward (Adams test, **Fig. 1B**). In thoracic scoliosis, vertebral rotation causes the rib angles to protrude, producing a posterior rib hump on the convex side with flattening of the anterior chest on the concave side **(Fig. 1C)**. In lumbar curves, the hip (pelvis) becomes prominent on the concave side. Associated findings can include breasts and shoulder level asymmetry, a sideways truncal shift and an apparent discrepancy in the leg-length. The

Table 1 Classification of scoliosis

Idiopathic
- Infantile
- Juvenile
- Adolescent

Congenital
- Failure of formation
  - Wedge vertebrae
  - Hemivertebrae
- Failure of segmentation
  - Unilateral bar
  - Block vertebra
- Mixed

Neuromuscular
- Neuropathic diseases
  - Upper motor neuron
    - Cerebral palsy
    - Spinocerebellar degeneration (Friedreich ataxia, Charcot-Marie-Tooth disease)
    - Syringomyelia
    - Spinal cord tumor
    - Spinal cord trauma
  - Lower motor neuron
    - Poliomyelitis
    - Spinal muscular atrophy
- Myopathies
  - Duchenne muscular dystrophy
  - Arthrogryposis
  - Other muscular dystrophies

Syndromes
- Neurofibromatosis
- Marfan syndrome

Compensatory
- Leg-length discrepancy
- Hip joint contractures

Source: Adapted from the Terminology Committee, Scoliosis Research Society: A glossary of scoliosis terms. Spine. 1976;1:57-8.

level and direction (convexity) of every curve is noted. Position of occiput can help differentiate balanced from unbalanced (or decompensated) curves. In the former, the occiput stays over the midline. Fixed curves become more obvious on forward bending, while postural curves are not aggravated. Spinal mobility and curve flexibility should be assessed. In the sagittal plane, the auricle and the shoulder should be centered over the greater trochanter. Any alteration due to excessive kyphosis or lordosis should be noted. A detailed neurological examination is important, to detect an underlying spinal cord lesion.

Imaging
Radiographs of the spine and iliac crests in posteroanterior (PA) and lateral views must be obtained, with the patient in erect posture. The degree of curvature is determined by the Cobb method in PA view; in which the angle between the superior and inferior end of vertebra is measured **(Figs 1D and E)**. The degree of curve correctability can be ascertained by X-rays in position of lateral bending.

Magnetic resonance imaging (MRI) may be indicated in the presence of (1) atypical history—early onset scoliosis, pain, rapid progression, neurological symptoms; (2) physical examination findings—neurological deficits, atypical curve patterns (left thoracic curve, double thoracic curves, high thoracic curves) and (3) atypical radiographic features (atypical curve patterns, vertebral anomalies, widening of the spinal canal, midline bony spurs, vertebral or rib dysplasia, and thoracic hyperkyphosis).

Skeletal age is helpful for planning treatment and should be assessed, as the deformity usually worsens during the period of rapid skeletal growth. The most common sites for assessment of skeletal age include the hand and wrist, acetabular triradiate cartilage, or iliac apophysis (*Risser's sign*).

Prognosis and Treatment
Treatment is directed at preventing worsening of the scoliosis and progressive fixed deformity. Prognosis of curve progression is the key in deciding the treatment. In general, the younger the child (more growth remaining years) and higher the curve, worse is the prognosis. Management differs for curves of different etiology, which are outlined below.

IDIOPATHIC SCOLIOSIS
About 80% of all cases of scoliosis are idiopathic in nature. Idiopathic scoliosis is further categorized according to the age of the child when the deformity was initially noticed. *Infantile scoliosis* presents between 0 year and 3 years of age. Juvenile idiopathic scoliosis (JIS) and adolescent idiopathic scoliosis (AIS) present between the ages of 4 years and 10 years and above 10 years, respectively. The three subtypes differ in terms of progression, prognosis and treatment strategies. Among the three variants, AIS accounts for 90% of all cases.

Etiology
Although the exact etiology of idiopathic scoliosis remains an enigma, many theories have been proposed over the years. Genetic factors, hormonal and metabolic dysfunction, neurologic dysfunction and biomechanical factors (asynchrony in spinal growth and anterior spinal overgrowth) have been implicated. In general, the etiology is considered multifactorial with a genetic predisposition.

Natural History
The natural history of idiopathic scoliosis depends on the age at presentation or diagnosis. Early onset (< 5 years) of idiopathic scoliosis is more likely to progress as compared to AIS. Thoracic curves greater than 50° and thoracolumbar or lumbar curves greater than 30° are likely to progress at approximately 1°/year throughout life. Curves greater than 70° result in chronic lung disease, and those above 100° may result in cor pulmonale and cardiorespiratory failure. Curves less than 30° rarely progress after skeletal maturity is achieved.

Infantile Idiopathic Scoliosis
Infantile idiopathic scoliosis (IIS) comprises a minority (< 1%) of idiopathic cases. Boys are affected more often. Most curves are thoracic with convexity to the left. Most infantile curves (90%) resolve on their own; the rest are progressive and can become severe. Infantile scoliosis affects the developing chest wall and respiratory system. Large curves before the age of 5 years may affect respiratory function and cause ventilation-perfusion mismatch.
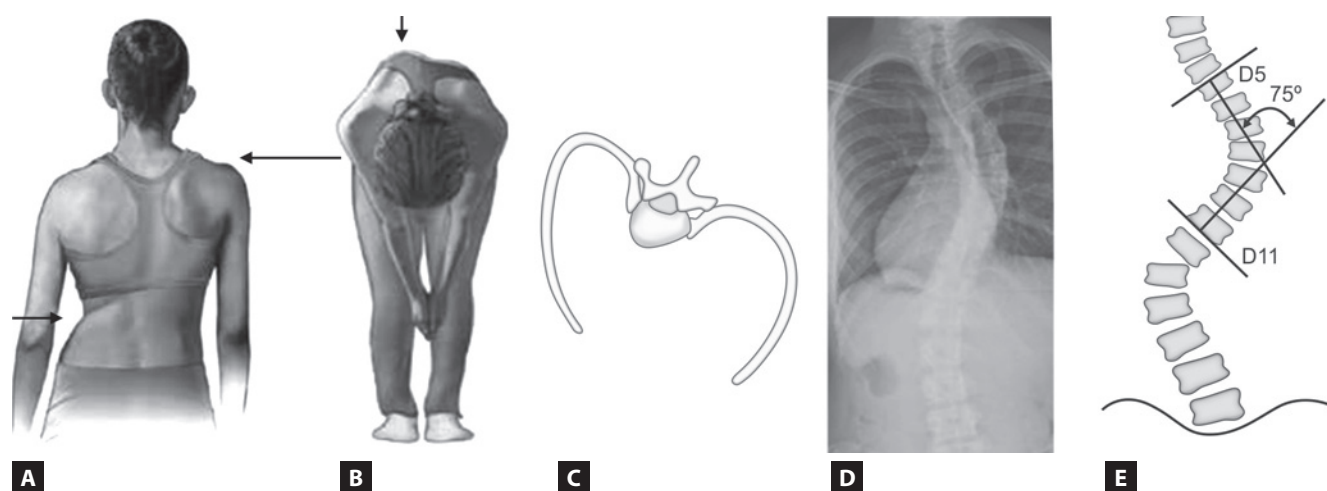
Figures 1A to E Clinical and radiograph findings in idiopathic scoliosis. (A) Clinical findings of asymmetry of shoulder height, scapular prominence, waistline, and elbow-to-flank distance are commonly seen; (B) On the Adams forward bending test, rib asymmetry of even a small degree is obvious; (C) Vertebral rotation with posterior displacement of the ribs on the convex side of the curve is responsible for the characteristic rib hump in patients with thoracic scoliosis; (D) Anteroposterior radiograph of a spine showing a right thoracic idiopathic scoliosis; and (E) Cobb method of curve magnitude measurement—A line is drawn across the superior endplate of each end vertebra, and the angle between perpendicular lines erected from each of these is measured

Management

Curves with a rib vertebral angle difference (RVAD) of 20° or more, Cobb angle of more than 25°, or a phase 2 rib head are highly likely to progress; these should be observed more closely. Curves with an RVAD of less than 20° and a phase 1 rib head usually are innocuous. MRI should be obtained for all curves of more than 20° to rule out associated anomalies of the brain and spinal cord.

Curves which are potentially progressive should undergo a clinical and radiographic evaluation at about 4–6-month intervals. An increase in Cobb angle of 5° or more over 6 months is an evidence of progression. Treatment may be initiated with scoliosis cast or corrective bracing. If the deformity continues to progress with an eventual Cobb angle of 45° or more, surgical correction may be considered, primarily to stop progression but includes correction of the existing curve and deformity. Surgical options include anterior or combined anterior-posterior spine fusion procedures. Newer options for managing IIS offer fusionless surgery, which includes distraction-based growing rods and growth directed surgery, (Shilla procedure), followed by definitive fusion at or near the end of skeletal growth. The purpose is to allow truncal growth and lung maturation while attempting to control the spinal deformity. More recent options are spinal tethering with non-metallic tethers, many of which are still experimental.

Juvenile Idiopathic Scoliosis

Juvenile idiopathic scoliosis (JIS) accounts for approximately up to 20% of idiopathic scoliosis. Girls are affected more often. Most abnormalities consist of right thoracic and double major curves. Patients with curves less than 20° require observation, with clinical evaluation and repeated erect PA radiographs every 4–6 months. If the curve increases, brace treatment is initiated. If the curve does not progress, child is kept under observation and follow-up until skeletal maturity. If orthotic treatment fails, surgery may be considered. In children less than 10 years of age, fusionless surgery is indicated. Fusion surgery is appropriate for older children. Both anterior and posterior spinal fusions may be considered together to avoid a crankshaft phenomenon.

Adolescent Idiopathic Scoliosis

Adolescent idiopathic scoliosis (AIS) accounts for 90% of idiopathic scoliosis cases and is more common in girls. Right thoracic and left lumbar are the principal curve patterns observed; thoracolumbar and double curves are less common.

Curves less than 20º are unlikely to progress. However, once the progression starts; it continues throughout the period of skeletal malnutrition. Knowledge of whether a scoliosis is likely to progress or not, is critical in deciding which patient requires treatment. Factors significant in assessing the risk for scoliosis progression include remaining skeletal growth, gender, curve magnitude and location.

Skeletal growth velocity is not uniform and there are the two phases of peak growth velocity (growth spurts)—early infancy and adolescence. In adolescence, the peak growth velocity averages 8–10 cm of height gain/year and half of this growth is contributed by the trunk (mainly the spine). Scoliosis progresses with growth and most rapidly during the growth spurts. Determining whether the patient has crossed the phase of peak growth velocity and the remaining skeletal growth is crucial to understanding the potential for curve progression. Several determinants aid in predicting the remaining growth including (1) indicators of skeletal maturity status as assessed by Risser's sign, status of the acetabular triradiate cartilage (open or closed); (2) menarchal status and (3) chronological age.

The Risser's sign is commonly used to assess the risk for progression of the curve. A Risser 0 or 1 implies the risk for progression is up to 60–70%. A Risser 3 implies the reduction of risk to less than 10% as the patient has crossed the phase of maximal growth and is in the plateau. Closure of the triradiate cartilage indicates that the patient has completed the phase of peak growth velocity. Menarche occurs approximately 12 months after the most rapid stage of skeletal growth. A postmenarche status implies that the patient has completed her growth spurt and hence risk for progression is relatively lower. The peak growth velocity is achieved between 10 years and 14 years in most girls, and between 12 years and 16 years in most boys. This range is too broad to make accurate predictions and, therefore, bone age is a more consistent indicator than chronological age.

Adolescent idiopathic scoliosis in girls is more likely to progress than in boys. Double curves are more likely to progress than single curves, and curves with an apex above T12 are more likely to progress than lumbar curves. The more severe the curve magnitude, higher is the risk of progression.

Treatment

The goals of treatment are: (1) to prevent a progression of deformity and (2) to correct an existing imbalance with deformity. The two major factors taken into consideration to decide the line of management are magnitude of deformity (as measured by the Cobb angle); and the potential for curve progression as determined by remaining skeletal growth.

Skeletally Immature Patients
- *Curve of less than 20°* Review every 6–9 months with standing PA radiographs to assess progression, which is defined as an increase of 5° or more.
- *Curve greater than 20°* Review every 3–4 months, with standing PA radiographs. If curve progresses beyond 25°, consider orthotic treatment.
- *Curves of 30–40°* Bracing is recommended. The goal is to prevent progression of the curve and reduce the requirement for surgery. Ideally the brace is to be worn for 23 hours/day; as the success of bracing depends on the time spent in the brace. However, concerns about patient compliance have led to part-time bracing regimens. An *in brace* correction of 50% in Cobb angle is desirable. There are several options for braces and the choice depends mainly on the level of the apex of the primary curve. When the apex is above T8, a Milwaukee brace is advised and if below T8, a Boston underarm brace is adequate. Bracing may not work in curves greater than 45°.
- *Progressive thoracic curves* greater than 45° or smaller lumbar or thoracolumbar curves with trunk shift and cosmetic deformity are candidates for surgery.

Skeletally Mature Patients
- *Curves of less than 20°* Generally do not require further evaluation.
- *Curve between 30° and 40°* Generally do not require treatment, but they should be followed on yearly basis for 2–3 years after skeletal maturity and then every 5 years thereafter.
- *Curves greater than 50°* These patients are candidates for surgery.

Exercises, spinal manipulation and electrical stimulation have been used to treat AIS, but robust evidence is lacking supporting their effectiveness. Exercise, however, helps to keep the spine supple.

Deformity correction is achieved using implants and fusion is performed to maintain it **(Fig. 2)**. The most common procedure is
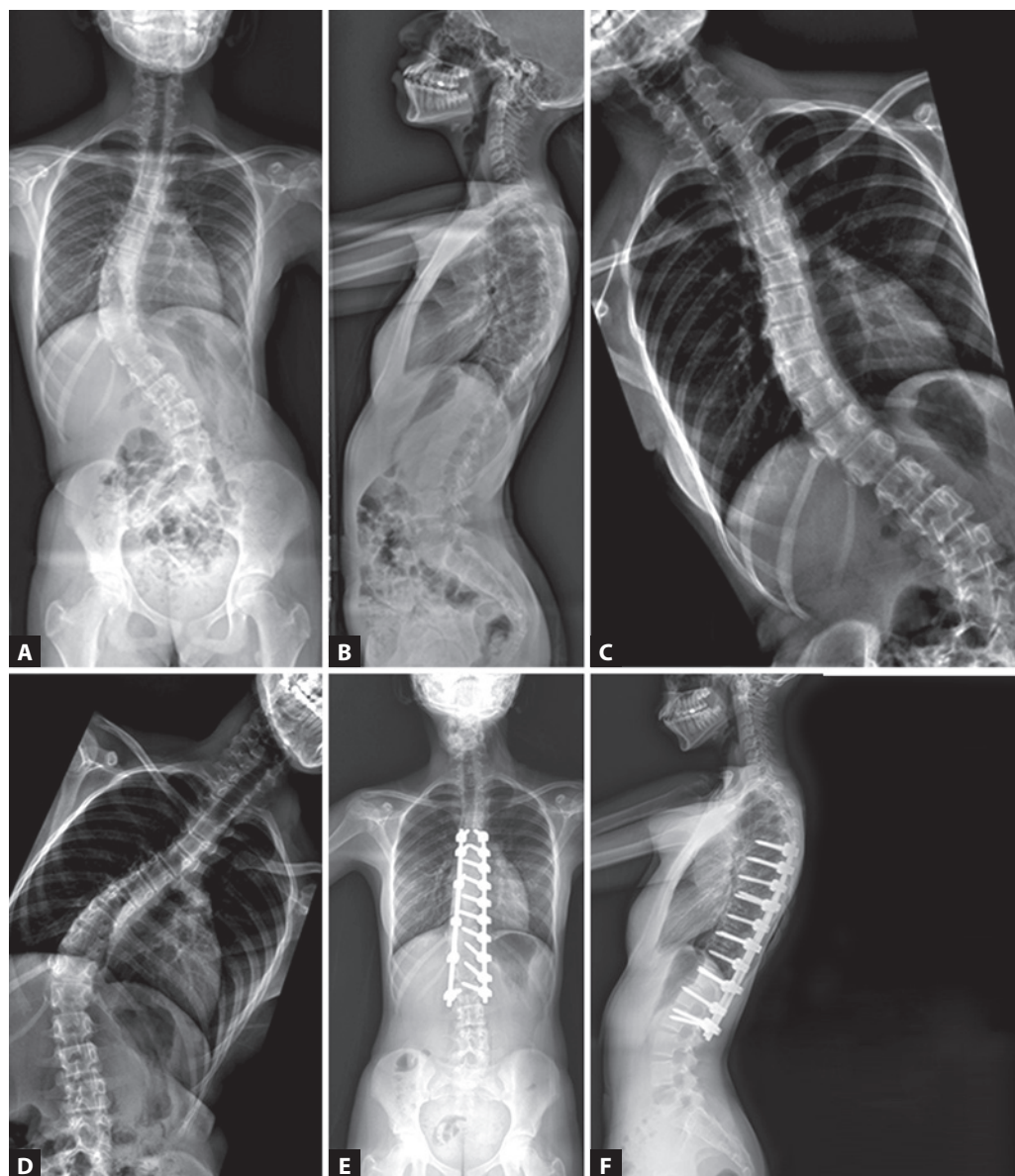
Figures 2A to F (A) Anteroposterior and (B) lateral radiographs of a 14-year-old girl with adolescent idiopathic right thoracic scoliosis; (C) right-side bending and (D) left-side bending radiographs to assess correctability of the curve; (E) anteroposterior and (F) lateral postoperative radiographs after a posterior pedicle screw instrumentation and fusion

an instrumented posterior spinal fusion using pedicle screws. An anterior release and fusion is indicated for isolated thoracolumbar and lumbar curves, to improve correctability of stiff large curves, and to prevent *crankshaft* in patients with considerable growth remaining. *Crankshaft* occurs from continued anterior spine growth in patients who have undergone a posterior spinal fusion (posterior tether).

Concerns regarding the long-term effects of decreased spinal mobility following spinal fusion have led to the use of novel fusionless methods such as stapling of the vertebral body and anterior tethering. The goal of using these techniques is to alter the remaining spinal growth of the child and achieve curve correction. The principle is based on the Hueter-Volkmann's law, in that compressing the convex anterior growth plates will inhibit their growth, while allowing the continued posterior and concave growth to ultimately reverse the deformity.

CONGENITAL SCOLIOSIS

Congenital scoliosis results from disordered vertebral formation occurring early in embryogenesis, presumably during somatogenesis between the 5th week and 8th week of gestation. Congenital vertebral anomalies may occur due to defects in formation, segmentation or a combination of both. Failure of formation may be partial (wedge vertebrae) or complete (hemivertebra), failure of segmentation may be partial (unilateral unsegmented bars) or complete (block vertebrae), a combination of both (unilateral unsegmented bar and contralateral hemivertebra) may occur **(Fig. 3)**. The bony anomalies can occur in isolation or in combination. The spine, neural elements and the viscera are formed around the 6th week of gestation, therefore children with congenital scoliosis are also likely to have other neuroaxial and visceral anomalies **(Table 2)**.
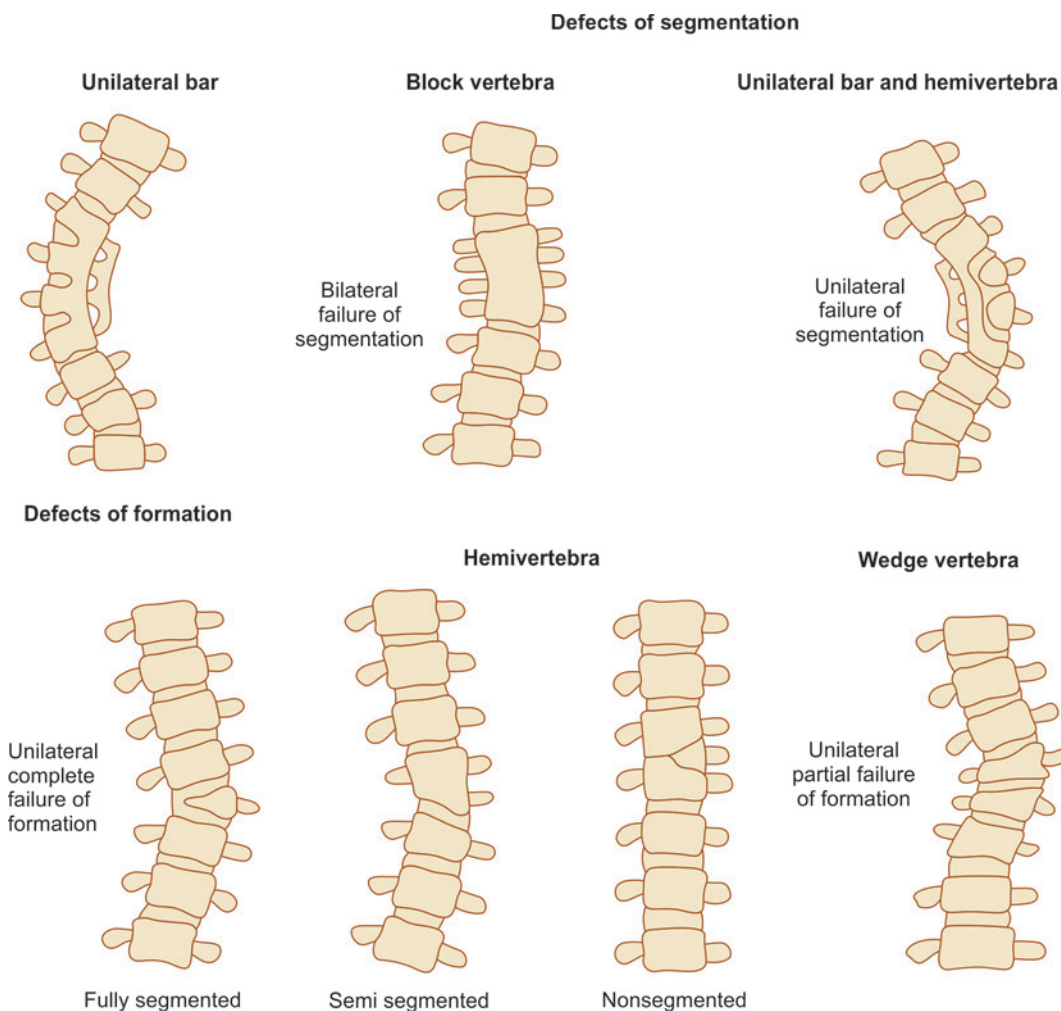
Figure 3 The defects of segmentation and formation that can occur during spinal development

Table 2 Visceral and intraspinal anomalies associated with congenital scoliosis

Visceral	Intraspinal
• *Genitourinary* (20–40% of children)	• *Spinal dysraphisms* (20–40% of children)
– Unilateral renal agenesis	– Diastematomyelia
– Ureteral duplication	– Split cord malformations
– Horseshoe kidney	– Intraspinal lipomas
– Genital anomalies	(intradural or extradural)
– Silent obstructive uropathy	– Arachnoid cysts
• *Cardiac* (10–25% of children)	– Teratomas
	– Dermoid sinuses
	– Fibrous bands
	– Tight filum terminale

Evaluation

A complete examination of the spine and nervous system is mandatory. Look for specific abnormalities on the back including cutaneous midline hair patches, lipomata, skin tags, dimples, sinuses and hemangiomas. Their presence may indicate an underlying closed spinal dysraphism. Closed spinal dysraphism may also cause tethering of the spinal cord, and present with back and/or leg pain, calf atrophy, and bowel or bladder dysfunction and progressive unilateral foot deformity.

All patients diagnosed with a congenital scoliosis should be screened for other organ anomalies. Renal ultrasonography

and an echocardiogram are routinely recommended by most clinicians.

Routine radiographs are essential to evaluate the deformity in terms of: degree of curvature (Cobb angle), site of the curve, and the morphology of the vertebral anomaly to analyze its growth potential and determine the risk of curve progression. CT scans are helpful to further delineate the vertebral anomaly, and myelography or MRI should be considered if neuroaxial abnormality is suspected.

Natural History

The rate of progression and the final magnitude of the curve are dictated by the type of anomaly and the site at which it occurs. A concave, unilateral unsegmented bar with a convex hemivertebra is the most progressive anomaly, followed by a unilateral unsegmented bar and a double convex hemivertebra. The severity of scoliosis is least with a block vertebra. The rate of deterioration is maximum for thoracolumbar anomalies, followed by those in the upper thoracic region. Curve progression occurs most rapidly during the two phases of peak skeletal growth velocity.

Management

Congenital scoliosis often is rigid and correction can be difficult. Early diagnosis and appropriate treatment while the curve is small is easier than performing salvage corrective procedures for severe deformities as the risk for neurological complications is high.

The treatment depends on (1) magnitude of deformity and (2) potential for curve progression which is determined by the type and site of anomaly **(Fig. 2)** and remaining growth. Assessing the potential for curve progression may not always be possible at initial evaluation (e.g., patients with multiple anomalies) and often a period of observation may be required. Small curves with low potential for progression are kept under observation. Bracing is ineffective for most congenital curves due to their structural nature. It is occasionally used to control flexible, compensatory curves that may occur above or below the rigid congenital scoliotic segment.

About 75% of congenital curves are progressive and surgery is the fundamental treatment. The treatment of progressive small curves is preemptive (before a significant deformity develops) spinal fusion and both anterior and posterior spinal fusion are often required. Isolated thoracolumbar or lumbar hemivertebra may be excised. Large curves require deformity correction by spinal osteotomy and instrumented fusion.

Thoracic insufficiency syndrome is the inability of the thorax to support growth of the lung and normal respiration. This syndrome is seen in (1) multilevel thoracic congenital scoliosis with multiple fused ribs on the concavity, (2) progressive infantile scoliosis with reduced thoracic volume from spinal rotation and (3) hypoplastic thorax syndromes, such as Jarcho-Levin syndrome and Jeune's syndrome. Thoracic cage deformity impairs lung development and function and may result in respiratory dysfunction and cor pulmonale.

Patients with multilevel fused ribs can be managed with an expansion thoracoplasty. Surgery is directed at correcting the chest wall deformity in a gradual manner, improving lung growth and function and correcting the associated spinal deformity. The procedure involves an opening wedge thoracostomy and placement of a vertical expandable prosthetic titanium rib (VEPTR) to achieve progressive lengthening of the chest wall on the concavity of the spinal deformity. Progressive infantile scoliosis is managed as described earlier.

NEUROMUSCULAR SCOLIOSIS

Neuromuscular conditions associated with scoliosis are enumerated in **Table 1**. Their etiology and natural history are different from idiopathic and congenital scoliosis.

Neuromuscular curves differ from idiopathic scoliosis in that (1) curves occur at a younger age, (2) most of these curves are progressive, (3) small curves can also progress even beyond the skeletal maturation, (4) these are less tolerant to orthotic management, and (5) surgery is associated with poor bone stock, longer fusions and increased blood loss.

Weakness and/or imbalance of the trunk musculature and loss of proprioception in the rapidly growing flexible spinal column are factors responsible for development of these curves. Spasticity plays a role in some patients. As the spine collapses, increased pressure on the concavity of the curve results in decreased growth (Hueter-Volkmann's law) of that side of the vertebral body resulting in a wedged vertebra. NMS is the most common in the nonambulatory populations who in general have a more global involvement.

The typical paralytic curve is long, C shaped, convex towards the side with weaker muscles (spinal, abdominal or intercostal) and frequently associated with pelvic obliquity. Severe pelvic obliquity may result in loss of sitting balance often necessitating the use of the upper limbs to sit. Pelvic obliquity in these patients may also occur due to hip joint and lower extremity contractures. In addition to the scoliosis patients with NMS, have additional problems of generalized muscle weakness and poor cardiopulmonary function and suboptimal nutritional status.

Treatment

The treatment of NMS depends on the magnitude of the curve, age of the patient, etiology, ambulatory status, mental status and the degree of progression of curve. Aim of the treatment is to maintain a straight spine over a level pelvis. Early intervention is desirable, before the spinal rigidity and the curve increase further. Small curves of less than 20–25° do not need immediate treatment and can be observed.

Progressive scoliosis in very young patients is treated with an orthosis. An orthosis will not arrest progression; however, it can slow the rate of progression and allow for further spinal growth before the definitive spinal fusion procedure. In nonambulatory patients with pelvic obliquity, orthoses improve sitting balance and tolerance freeing the upper extremity to function, and combined with seating modification improve ease of care. The standard braces used for idiopathic scoliosis are poorly tolerated in these patients. Patients with trunk control can be prescribed a custom-made, total-contact thoracolumbar-sacral orthosis (TLSO), however, patients with severe involvement and no head control usually require custom-fabricated seating devices combined with orthoses or head-control devices.

In general, surgery is offered to patients with progressive curvatures greater than 40–50°. Patients who are ambulatory and require lumbosacral movement are fused from the upper thoracic spine (usually T4) down to L5. Nonambulatory patients will need a spinal fusion extending to the pelvis.

SCOLIOSIS DUE TO SYNDROMES AND GENETIC DISORDERS

Many syndromes and genetic disorders include scoliosis as an important manifestation. These include several neurocutaneous syndromes, skeletal dysplasias, and connective tissue and collagen disorders (Marfan syndrome, Ehlers-Danlos syndrome). The management is based on the patient's age, curve magnitude, potential for progression and underlying etiology.

Scoliosis in neurofibromatosis may be *dystrophic* (deformity due to dystrophy of the vertebrae and ribs) or *nondystrophic* (mimic idiopathic scoliosis). A dystrophic scoliotic curve is typically *short, sharp and angular* and large curves may have neurological deficits. Nondystrophic curves have the same prognosis, evolution and general guidelines for management as do idiopathic curves except that they have a higher risk of developing a pseudoarthrosis after fusion. For the typical dystrophic curve of neurofibromatosis there is no role for brace treatment. Need for surgery is dictated by the presence of neurological deficits, or a kyphotic deformity.

KYPHOSIS

Kyphosis is the normal gentle rounding (convex posterior) of the thoracic spine. However, the term is often used to describe the abnormal/increased thoracic curvature or reversal (loss) of cervical or lumbar lordosis. Excessive thoracic curvature is better described as *hyperkyphosis*.

Postural Kyphosis

Postural kyphosis is a painless hyperkyphosis common in adolescence. The curve is a long one and the deformity can be corrected voluntarily by the patient. The physician's role is to rule out structural causes of kyphosis such as Scheuermann's disease and neurofibromatosis. When bending forward patients with postural round back are noted to have a gentle rounding of the back, while patients with Scheuermann's disease **(Fig. 4)** and neurofibromatosis have a sharp angular kyphosis. Radiographs are usually necessary in order to rule out pathologic types of kyphosis.
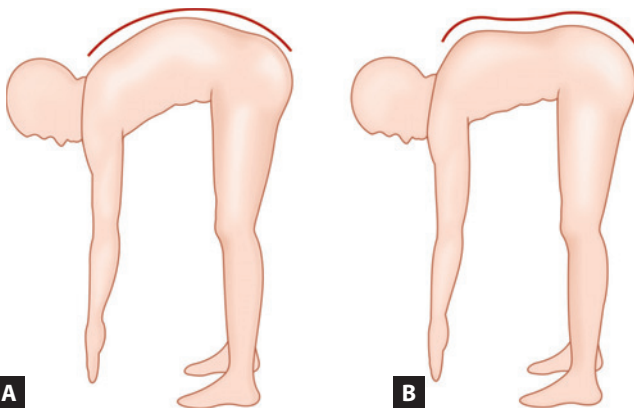
Figures 4A and B (A) Side on view of normal spinal contour on forward bending and (B) Side on view of a patient with Scheuermann's disease on forward bending. A sharp angular kyphosis of the spine is observed

The prognosis is good and treatment consists of posture training and exercises. Bracing is not recommended.

Structural Kyphosis

Structural kyphosis is fixed and associated with changes in the shape of the vertebrae. The common causes are enumerated in **Table 3**.

SCHEUERMANN'S DISEASE (ADOLESCENT KYPHOSIS, VERTEBRAL OSTEOCHONDRITIS)

Scheuermann's disease is a structural kyphosis affecting the thoracic or thoracolumbar spine. It is further categorized in a typical and an atypical form. *Typical Scheuermann's disease* involves the thoracic spine and has the classical radiographic features of wedging (5° or more) of three or more consecutive vertebrae producing kyphosis. *Atypical Scheuermann's disease* usually involves the lumbar spine the thoracolumbar junction. Characteristic radiological features include; vertebral endplate changes, narrowing of disc space and anterior Schmorl's nodes.

Table 3 Etiology of kyphosis

Kyphosis
- Nonstructural kyphosis
  – Postural kyphosis
- Structural kyphosis
  – Scheuermann's kyphosis
  – Congenital kyphosis
  – Postinfectious kyphosis—Tuberculosis, other infections
  – Neurofibromatosis
  – Post-traumatic kyphosis
  – Myelomeningocele
  – Paralytic disorders—Poliomyelitis, anterior horn cell disease
  – Developmental—Achondroplasia, mucopolysaccharidosis, others
  – Postsurgical—Postlaminectomy, inadequate fusion
  – Metabolic—Infantile idiopathic osteoporosis, secondary types of osteoporosis, osteogenesis imperfecta
  – Tumor—Benign, malignant
  – Postirradiation for tumors

Hyperlordosis
- Structural
  – Neuropathic
  – Congenital

Etiology

The etiology of Scheuermann's disease is probably multifactorial. Scheuermann proposed that osteonecrosis of the vertebral body ring apophysis resulted in wedging and kyphosis and termed it as *vertebral osteochondritis*. Schmorl suggested that herniation of disc material into the vertebral body resulted in vertebral wedging while Ferguson implicated that the persistence of anterior vertebral body vascular grooves during preadolescence create a point of structural weakness in the vertebral body, leading to wedging and kyphosis. Others have suggested that a biochemical abnormality of the collagen and matrix of the vertebral endplate cartilage may be important in the etiology. The true nature of the disorder is still not known and requires further investigation.

Clinical Features

The age at onset usually is during the prepubertal growth spurt, between 10 years and 12 years of age and affects boys more often than girls. Commonly, the presenting complaint is poor posture as noted by the parents or the patient may complain of backache and fatigue. Clinically the patient has an abrupt kyphosis, which is more apparent with forward bending and does not correct with the prone extension test. Below, it is a compensatory lumbar lordosis. A mild scoliosis is not uncommon. Movements are normal. Neurologic examination is usually normal, although neurologic deficits have been reported in patients with thoracic disc herniation and progressive kyphosis.

Investigations

Lateral radiographs of the spine show irregularity and fragmentation of vertebral endplates of several adjacent vertebrae with anterior wedging of one or more vertebral bodies. Schmorl's nodes (small radiolucent defects in the subchondral bone) may also be observed. The criteria for the diagnosis of typical Scheuermann's disease are: (1) more than 5° of wedging of at least three adjacent vertebrae at the apex of the kyphosis and (2) vertebral endplate irregularities with a thoracic kyphosis of more than 50° **(Fig. 5)**.
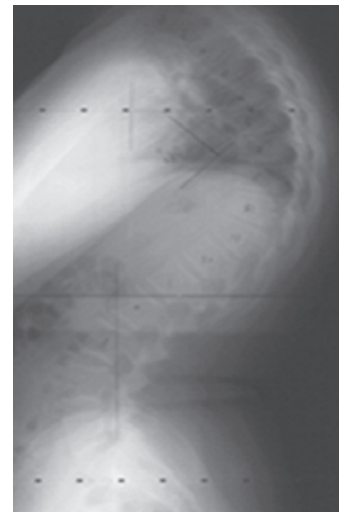
Figure 5 Radiograph of typical Scheuermann's kyphosis. Wedging of more than 5° in at least three adjacent vertebrae with vertebral endplate irregularities at the apex of the kyphosis is seen

Differential Diagnosis

Postural kyphosis, the major differentiation from a postural roundback is that the deformity is more abrupt and relatively inflexible. Mild cases of spondyloepiphyseal dysplasia can produce changes at multiple levels similar to those of Scheuermann's disease; however, they have associated characteristic defects in other joints.

Treatment

Adolescents with mildly increased kyphosis which is less than 50° are followed up (till completion of growth) at 4–6 months intervals with standing lateral radiographs to assess for progression. Back-strengthening exercises and postural training can help to maintain flexibility, correct lumbar lordosis; however, curve correction cannot be expected. Curves of more than 50° in skeletally immature patients are managed with a spinal orthosis (like Milwaukee brace). Surgical indications for correction of Scheuermann's kyphosis include (1) progressive deformity of more than 75°, (2) neurologic deficit, (3) persistent pain despite aggressive conservative management and (4) cosmesis especially when it is causing severe psychosocial issues in patients.

CONGENITAL KYPHOSIS

Congenital kyphosis implies a defect in spinal column development from a failure of vertebral formation (type I, hemivertebra), failure of vertebral segmentation (type II, anterior unsegmented bar, block vertebra) or a combination of the two (type III, anterolateral bar with contralateral quadrant vertebra), resulting in a sagittal plane deformity **(Fig. 6)**. Vertebral malformation may result in an isolated sagittal plane deformity, though these are most often combined with a scoliosis.

Classification

Type I is the most common type and most often occurs in the thoracic region. An anterior failure of vertebral body formation produces a sharply angular progressive kyphosis and posterior displacement of the hemivertebra may lead to cord compression. Type II usually takes the form of an anterior intervertebral body bar. Continued growth of the posterior elements causes the affected segment of the spine to gradually become kyphotic. There is a much lower chance of neurologic dysfunction. Type III is mixed anomalies and progression is most rapid in this type. The risk of neurological deficit is highest in type I and III because they tend to have an acute angular kyphosis over a short segment.

Clinical Features

Patients with congenital kyphosis may have associated intraspinal anomalies (19–29% of children) and nonskeletal anomalies such as cardiac, pulmonary, renal and auditory disorders. Progression of the kyphotic deformity is determined by the type of vertebral malformation, the number of vertebrae involved and the amount of remaining normal growth in the affected vertebrae. The greatest rate of progression occurs during the time of most rapid growth of the spine (birth to 3 years of age) and during the adolescent growth spurt.

Figure 6 Congenital vertebral anomalies that result in kyphosis or kyphoscoliosis
Source: Reproduced with permission from McMaster MJ, Singh H. Natural history of congenital kyphosis in kyphoscoliosis: a study of one hundred and twelve patients. J Bone Joint Surg. 1999;81:1367-83.

Diagnosis

While routine radiographs can most often adequate to delineate the vertebral anomaly, CT scan with reconstruction views is required in the presence of mixed anomalies, large curves, contiguous multilevel anomalies and especially if surgery is planned. A screening magnetic resonance image of the whole spine is recommended, as is evaluation of the urogenital and cardiac systems to identify other organ system abnormalities. Congenital kyphosis, as well as associated renal problems, can be seen on routine prenatal ultrasonography at as early as 20 weeks of gestation.

Treatment

The treatment depends on the type of vertebral malformation, the magnitude of deformity and neurological status. Standard nonoperative management includes close observation and reassessment every 4–6 months to monitor curve progression and detect any early abnormal neurologic changes. Bracing has no role in the treatment of congenital kyphosis, except to keep the compensatory curves above or below the kyphotic segment supple and/or slow their progression. Surgery is the only effective treatment option for progressive curves or those with a poor natural history (type I), and it typically involves a spinal fusion. For type I deformities in patients younger than 5 years with a deformity of less than 50° and no neurological deficits, a posterior fusion is appropriate. A solid posterior fusion allows any remaining anterior physes to continue to grow, which may result in some degree of spontaneous reduction of the kyphosis during the growing years. Patients with severe deformity and/or neurological deficits require anterior vertebral remnant excision for spinal cord decompression, deformity correction and fusion. If an intraspinal abnormality is detected by MRI, it should most often be addressed before surgical correction of the kyphosis.

SPINAL TUBERCULOSIS

In India and the developing world, spinal tuberculosis (TB) is the most common cause of postinfectious spinal deformity. Lower thoracic and lumbar regions are more frequently involved, whereas the cervical region is rarely involved. Anterior region of the vertebral body is involved in 90% of the cases. Posterior vertebral elements are rarely involved in an isolated manner.

Pathology

Tubercle bacilli spread hematogenous and most often localize in the paradiscal region of adjacent vertebra. Caseous necrosis and bone destruction is followed by intervertebral disc destruction. A pre- and paravertebral abscess may form, and spread along muscle and neurovascular planes. Cold abscess may be seen in Petit's triangle or anterior femoral triangle. The disc space narrows. It is followed by progressive collapse of vertebral bodies into each other. This results in a sharp angulation in the spine (gibbus or kyphos). The collapse is progressive until healing occurs. Spinal cord dysfunction may occur due to compression by an abscess, granulation tissue, sequestra or displaced bone, or occasionally ischemia from spinal artery thrombosis. Vertebrae recalcify with healing and may fuse together. In children, the kyphotic deformity may progress with growth. Severe kyphotic deformities in healed TB may predispose to late onset neurological deficits.

Paraplegia in spinal TB may occur during active disease or healed stage. Paresis occurring within 2 years of onset of disease (*early-onset paresis*) results either from inflammatory edema or pressure by an abscess, granulation tissue or bone sequestra.

Late onset paresis occurs in the healed stage and is due to direct cord compression from the internal gibbus, increasing deformity, or vascular insufficiency of the cord. Prognosis for neurological recovery following surgery in early onset paresis is good; however, it is poor in late onset paresis.

Clinical Features

These patients usually present with failure to thrive and back pain and occasionally a gibbus deformity. An occasional child may present with a cold abscess in the groin, Petit's triangle, sacroiliac joint region. A *pseudo* hip flexion deformity may present secondary to a psoas abscess. They may present with lower limb paresthesia and weakness if there is neural compression. Most children under 10 years with thoracic spine involvement will have concurrent pulmonary TB. Clinically, there is local spinal tenderness with or without a gibbus and painful restriction of spinal movements. Lower limbs may show motor and/or sensory changes.

Imaging

On radiographs, the earliest signs of infection are localized rarefaction of two adjacent vertebrae, fuzziness and erosions of the endplates and narrowing of the intervertebral disc space. As the disease progresses, vertebral body destruction is visible. There may be an evidence of paravertebral abscess. The radiological picture may need to be differentiated from many other fungal and parasitic infestations. With treatment, bone density increases, paravertebral abscesses resolves, and vertebral fusion may occur. MRI scans provide more information about the extent of involvement, presence of paraspinal/epidural abscesses, detect hidden lesions, provide sufficient detail to guide the need for invasive diagnostic procedures, and help in monitoring disease process and response to treatment.

Tuberculin test may be positive. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be raised in the acute stage and though nonspecific are useful to detect response to treatment. A needle/core biopsy is recommended to confirm the diagnosis by histological and microbiological investigations.

Treatment

The objectives are to: (1) control and eradicate the disease; (2) prevent or correct deformity and (3) prevent or treat neurological deficit. Early diagnosis and antituberculous chemotherapy are critical. Surgical treatment may be considered as an adjuvant to effective drug therapy. Ambulant chemotherapy may be considered for early or limited disease in a stable spine with no neurological deficit. Treatment is continued for 9–12 months depending on the regimen chosen. Conservative treatment alone may carry the risk of progressive kyphosis and regular radiographic monitoring may be required to assess progression of deformity and for the *spine at risk signs*.

The radiological *spine at risk signs* was described to potentially identify children who were at risk to develop severe deformity. A severe kyphotic deformity can lead to cardiopulmonary compromise and late onset neurological deficit. Prevention of the deformity is important as management of an established deformity is more complicated than preventive surgery. Children 10 years of age or less are more susceptible to experiencing progressive deformity with the disease. Risk signs are as follows: facet joint separation, posterior retropulsion of the diseased segment, lateral translation of the vertebral column, toppling of the cephalad over the caudal vertebra. The presence of two or more signs is indicative of instability and prognosticates the development of severe deformity. These patients will benefit from early surgery.

Surgery in active disease is indicated: (1) when there is an abscess causing pressure symptoms that requires to be drained; (2) severe kyphosis; (3) for neurological deficit including paraparesis that has not responded to drug therapy; or (4) in presence of two or more *spine at risk signs*.

MORE ON THIS TOPIC

Batra S, Ahuja S. Congenital scoliosis: management and future directions. Acta Orthop Belg. 2008;74:147-60.

Campbell RM, Smith MD, Mayes TC, et al. The characteristics of thoracic insufficiency syndrome associated with fused ribs and congenital scoliosis. J Bone Joint Surg Am. 2003;85:399-408.

Gillingham B, Fan RA, Akbarnia BA. Early onset idiopathic scoliosis. J Am Acad Orthop Surg. 2006;14:101-12.

Lowe TG, Line BG. Evidence based medicine: analysis of Scheuermann kyphosis. Spine (Phila Pa 1976). 2007;32:S115-9.

McMaster MJ, Singh H. Natural history of congenital kyphosis in kyphoscoliosis: a study of one hundred and twelve patients. J Bone Joint Surg. 1999; 81:1367-83.

McMaster MJ, Singh H. The surgical management of congenital kyphosis and kyphoscoliosis. Spine (Phila Pa 1976). 2001;26:2146-54.

Richards BS, Vitale MG. Screening for idiopathic scoliosis in adolescents: An information statement. J Bone Joint Surg Am. 2008;90:195-8.

Weinstein SL, Dolan LA, Cheng JC, et al. Adolescent idiopathic scoliosis. Lancet. 2008;371:1527-37.

IN A NUTSHELL

1. Scoliosis can occur due to varied etiology, idiopathic being the most common. Treatment strategies differ depending on the etiology.

2. Factors significant in assessing the risk for progression of scoliosis include remaining skeletal growth, curve magnitude at presentation and curve location. Remaining growth may be determined using (1) indicators of skeletal maturity status as assessed by Risser's sign, status of the acetabular triradiate cartilage (open or closed); (2) menarchal status and (3) chronological age.

3. Early onset scoliosis can affect the pulmonary development and result in cardiopulmonary function compromise. These patients need early referral and intervention.

4. Patients with congenital scoliosis may have associated neuroaxial and visceral (cardiac, urogenital) anomalies and they should be assessed for the same.

5. Spinal tuberculosis is a common etiology of kyphosis in the developing world. Antituberculous therapy is indicated: (1) when there is an abscess causing pressure symptoms that requires to be drained; (2) severe kyphosis; (3) for neurological deficit not improving with drug therapy; or (4) in presence of two or more spine at risk signs.

Chapter 49.6
Developmental Dysplasia of the Hip (DDH)

Venkatadass K, Harish S Hosalkar

In majority of pediatric orthopedic literature, the term congenital dislocation of hip (CDH) has been replaced by developmental dysplasia of hip (DDH). The American Academy of Pediatrics defines developmental dysplasia of the hip as a condition in which the femoral head has an abnormal relationship to the acetabulum. This is mainly related to the shallowness of the acetabulum and therefore a possible mismatch between the two articulating surfaces of the femur and the acetabulum, with or without a component of instability. DDH is therefore a wide spectrum that includes mildly shallow acetabulum (acetabular deficiency only) with a well-located femoral head at one end, to *subluxation* (partial loss of contact between the articular surfaces), or frank *dislocation* (complete loss of contact between the articular surfaces) at the other end.

Another distinct form of hip dislocation is termed *teratologic dislocation* wherein the dislocation occurs much before birth. These babies often have stiff a hip with limited range of motion, and the hips may not be reducible on examination. Teratologic dislocation of the hip can be associated with other neuromuscular problems, especially those related to muscle paralysis, such as myelodysplasia and arthrogryposis. It may also have a syndromic association.

INCIDENCE

The incidence of frank dislocation at birth is approximately 1–1.5 per 1,000 live births whereas the incidence of dysplasia or instability is as high as 1 per 100 newborns. There are of course regional and geographic variations described. Ultrasound studies have demonstrated dynamic hip instability and/or ultrasonographic hip dysplasia in up to 5% to 15% of all newborns. Geographical and racial variations in the incidence exist which is mainly due to the child rearing practices rather than genetic pre-disposition. African and Asian caregivers traditionally carry the babies against their bodies, so that the child's hips are flexed, abducted and free to move. This is the optimal position for stability and also for development of acetabulum by the cartilaginous femoral head, which may account for lower incidence of the problem. Native American and European children have a high incidence of DDH due to the swaddling culture, which places the hip in extension.

ETIOLOGY AND RISK FACTORS

Developmental dysplasia of hip seems to evolve over time. The structures that make up the hip are possibly normal during embryogenesis and gradually could become abnormal for a variety of reasons, chiefly fetal position and presentation at birth (malposition of the femoral head, abnormal forces acting on the developing hip) and laxity of the ligamentous structures about the hip joint.

The etiology of DDH is multifactorial, involving both genetic and intrauterine environmental factors **(Box 1)**. The following are reported as risk factors for DDH (despite lack of robust evidence for some individual factors):

- *Family history* Positive in up to12–33% of affected patients.
- *Females* About 80% of cases are females; this is likely due to greater susceptibility of girls to maternal relaxin hormone, which increases ligamentous laxity.

- *First born* Potentially, related to tight intrauterine space and less room for fetal motion.
- *Breech* 16–25% of babies with DDH may have history of breech presentation; extended knee position likely increases the tension in hamstrings and destabilizes the hip.
- *Associated anomalies* Torticollis, and metatarsus adductus. Intrauterine crowding may the reason.
- Oligohydramnios and high birthweight are also proposed factors.

CLINICAL PRESENTATION (BOX 2)

Neonate
Ortolani and Barlow are the standard tests used for diagnosing DDH in the neonate and infant.

Barlow Test
This is a provocative maneuver to assess an unstable but contained hip. The baby is placed supine on the couch and should preferably be settled. The hips and knees are flexed to 90º and the examiner holds both the thighs with thumb on the medical aspect and three fingers on the lateral aspect. Both the hips are gently adducted and posterior thrust is given to dislocate the femoral head. A palpable dislocation with the *clunk of exit* indicates a positive test **(Fig. 1)**.

In dysplastic but so-called stable hips, one may perform this maneuver in different degrees to hip flexion and adduction to test for the sectoral deficiency in the acetabulum (Senior author's personal experience).

Ortolani Test
Also called as "sign of the ridge" is the reverse of Barlow and the examiner attempts to reduce a dislocated hip. The baby is positioned similarly to that in Barlow maneuver and the hip is gently abducted. The examiner holds the baby's thigh between the thumb and index finger and, with the fourth and fifth fingers lift the greater trochanter while abducting the hip. In a positive test, the femoral head slips into the acetabulum with a palpable *clunk of entry* **(Fig. 2)** this should a gentle and non-forced maneuver.

BOX 1 Risk Factors for DDH

- Breech presentation
- Female gender
- Positive family history
- Torticollis
- Metatarsus adductus
- Oligohydramnios
- Hip asymmetry

BOX 2 Clinical signs by age in DDH

Neonate
Dislocatable (Barlow's test)
Reducible (Ortolani test)

Infant
Dislocatable (occasionally)
Reducible (occasionally)
Galeazzi's sign
Decreased abduction

Walking child
Remains dislocated
Galeazzi's sign
Decreased abduction
Limp
Shortening
Increased lordosis (bilateral)
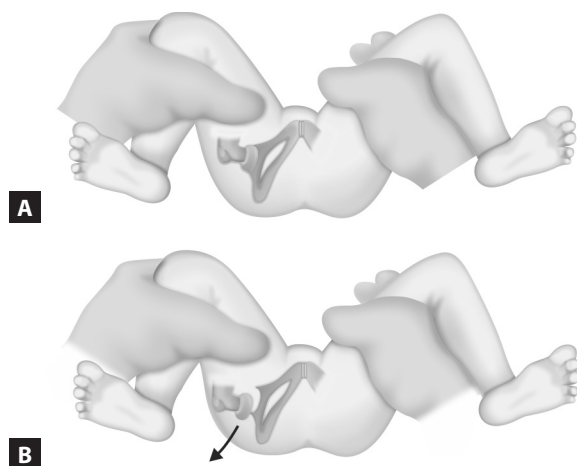
Figures 1 Barlow test. (A) The child is positioned supine and the examiner holds both the thighs with hips and knees in flexion and with the thumb on the medial aspect of thigh the limb is gently adducted and a posterior thrust is given; (B) A positive test is felt by the head dislocating posteriorly which is termed as the "clunk of exit"

Figure 2 Ortolani test. (A) The child is positioned supine and the examiner holds both the thighs with hips and knees in flexion with the thumb on the medial aspect and three fingers on the lateral aspect of thigh; (B) The limb is gently abducted and the greater trochanter is pushed up which relocates the head into the acetabulum felt as "clunk of entry"

Hip click refers to the *clicking* sensation felt during abduction-adduction movement. It usually originates from the ligamentum teres, tensor fascia lata or psoas tendon and may not indicate a true hip pathology. It is important to realize that most referrals to orthopedic surgeons/hip specialists are based on the diagnosis of the hip-click by the parent/pediatrician and as such it is important to examine these children to potentially identify that segment of population that may have true DDH. It should be differentiated from *hip clunk*, which is heard and felt as the hip goes in and out of the joint.

Infant
Unilateral dislocation produces a visible asymmetry in abduction on the affected side compared to the other side. This is due to shortening of adductor longus associated with hip dislocation.

Galeazzi Sign
Both the hips and knees are placed in 90 flexion and both the feet are made to rest on the firm surface. An asymmetry between the levels of the two-knee joints is indicative of positive test.

Asymmetry of thigh and gluteal folds should alert the physician to perform a thorough exam to identify or rule out DDH. In children with bilateral dislocation combined abduction is limited, but need not be asymmetric. This can be tricky sometimes and on occasion DDH in bilateral cases may be missed or diagnosed late for these reasons. With an index of suspicion it is prudent to obtain imaging ultrasound in these patients.

Walking Child
A walking child with undetected DDH may present with a limp, waddling gait or limb length discrepancy. The affected side is shorter and child may usually toe-walk on the affected side. There is usually limited abduction on affected side and a positive Galeazzi sign. The Trendelenburg sign is often positive and the child walks with Trendelenburg gait. Excessive lordosis may develop due to hip flexion contracture.

DIAGNOSTIC IMAGING

Ultrasonography
The predominantly cartilaginous acetabulum and proximal femur in infants less than 6 months of age are best visualized with ultrasonography. In addition to morphologic assessment, ultrasonography provides dynamic assessment about the stability of the hip joint. The ultrasound examination is also helpful to monitor acetabular development in infants treated with Pavlik harness. The distinct advantage of ultrasonography is that it provides some anatomic evaluation of the hip joint without exposing the infant to radiation.
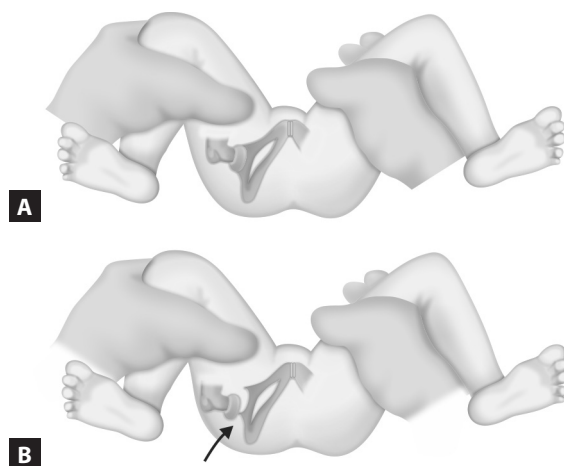
The indication for the universal use of ultrasound in DDH is not clearly established. The practice varies in different institutions across the globe. In Europe, it is used as a routine screening tool for all newborn. However, there are studies that suggest caution that routine use of ultrasound screening may result in overdiagnosis and overtreatment of DDH. The current practice in India is to use USG for screening (A) at-risk babies, (B) newborns with clinical signs of DDH, and (C) newborns with other associated anomalies to rule out DDH.

Radiography
Radiographs are usually recommended for an infant after 4 months of age when the proximal femoral epiphysis ossifies. Several radiographic features and traditional measurements have been described on a routine anteroposterior (AP) view of the pelvis **(Fig. 3)**.

- The *Hilgenreiner line* is a horizontal line drawn through the top of the triradiate cartilage. The *Hilgenreiner point* is the central point of the most prominent proximal femoral metaphysis visible on the radiograph. The *Perkins line* is a vertical line through the most lateral ossified margin of the roof of the acetabulum perpendicular to the Hilgenreiner line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these two lines.
- The *Shenton line* is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus and it forms a smooth arc in a child with normal hips. In a child with DDH, this line consists of two separate arcs and therefore is described as *broken* **(Fig. 4)**.
- The *acetabular index* is the angle formed between the Hilgenreiner line and a line joining the lateral most ossified margin of the roof of the acetabulum from the triradiate cartilage. This angle measures the development of the osseous roof of the acetabulum. In the newborn, the acetabular index can be up to 40° and by 4 months it usually subsides to 30° or less.
- In the older child, the *center-edge angle* is a useful measure of the lateral coverage of the femoral head. This angle subtended
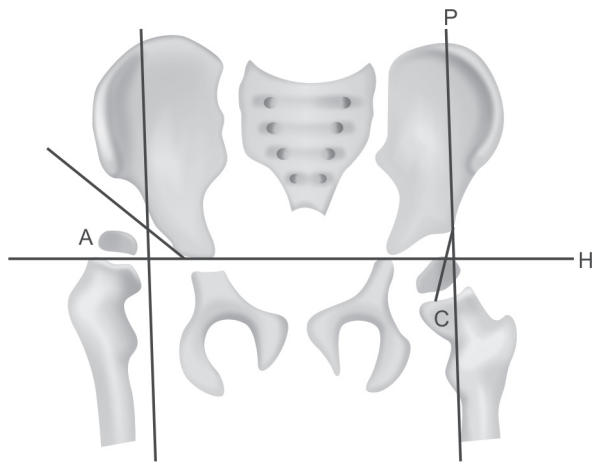
Figure 3 Diagrammatic representation of the radiological parameters in DDH. H: Hilgenreiner line is a horizontal line connecting both the triradiate cartilages. P: Perkin's line the vertical line drawn perpendicular to the Hilgenreiner line at the outermost edge of the acetabulum. The ossific nucleus of the femoral head should be located in the lower and inner quadrant of the intersection of these two lines. A: Acetabular index is the angle between the Hilgenreiner line and a line joining the lateral most ossified margin of the roof of the acetabulum from the triradiate cartilage. C: Center edge angle of wiberg is the angle subtended between the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head
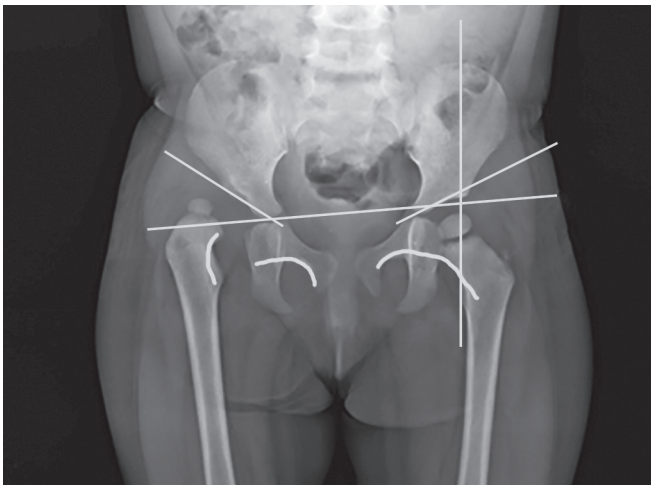
Figure 4 Anteroposterior radiograph of a 2-year old child with DDH of right hip. The right hip shows break in the Shenton's line and increased acetabular index (40°)

between the Perkin's line and a line connecting the lateral margin of the acetabulum to the center of the femoral head. In children 6–13 years old, an angle of approximately 20 and more degrees has been reported as normal, while in children 14 years and older, an angle more than 25° is considered normal.

MRI

Magnetic resonance imaging (MRI) is a useful tool for diagnosis and evaluation, as well as for documentation of femoral head and acetabular relationships after closed or open reduction. The need for anesthesia in infants and children limits its utility. MRI with cartilage imaging sequences has a definitive role in managing residual dysplasia in older children and adolescents before planning for hip preservation procedures.

BOX 3 Guidelines for treatment of DDH

- *0–6 months:* Apply Pavlik harness for 6 weeks with the hip in reduced position
- *6 months–2 years:* Closed/Open reduction and Spica cast for 3 months
- *Older than 2 years*: Open reduction with femoral osteotomy + acetabular procedures.

MANAGEMENT

The primary aim of management of DDH is to achieve a stable and concentric reduction, which thereby would help in as close to normal development of the acetabulum and proximal femur as possible. This has to be achieved as early as possible either by closed or open methods to ensure normal development of the hip **(Box 3)**. In general, the later the diagnosis or presentation, the more difficult it would be to achieve a good reduction and more complex the intervention would be to contain the hip.

Newborn and Infants Younger than 6 Months

When the diagnosis of DDH is made during neonatal screening (which is ideal) the treatment should be started immediately. Pavlik harness is the most common orthosis used to treat an Ortolani or Barlow positive hip. When appropriately applied, the Pavlik harness prevents the hip extension and adduction that can lead to redislocation, but it allows further flexion and abduction, which lead to reduction and stabilization. By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for up to 6 weeks, hip instability resolves in 95% of cases.

The Pavlik harness can be used until 6 months of age for any child with residual dysplasia, subluxation, or complete dislocation. After 6 months of age, the failure rate for the Pavlik harness may be much higher because it is difficult to maintain the increasingly active and crawling child in the harness. Ultrasound evaluation is very useful to look at the status of the hip after Pavlik harness application. If the hip remains subluxed or dislocated with Pavlik harness in-situ, the possibilities are that either the device is applied inappropriately or that the hip is irreducible and needs other form of treatment. Inappropriate application/usage of Pavlik harness can be associated with complications including damage of the cartilaginous femoral head and the proximal femoral physeal plate.

6 Months to 2 Years of Age

For children older than 6 months of age at diagnosis or those who have failed a trial of Pavlik harness treatment, closed reduction may be indicated. Closed reduction is usually performed in the operating room under general anesthesia. Arthrogram is very useful to assess and document the obstacles to reduction as well as study the adequacy of reduction. After achieving a stable reduction, it needs to be maintained by a well-molded hip spica cast for up to 12 weeks. Failure to obtain a stable hip by closed reduction indicates the need for an open reduction. In patients younger than 2 years of age, a secondary acetabular or femoral procedure is rarely required. The potential for continued acetabular development after closed or open reduction is excellent and continues for up to 4–8 years after the procedure.

Older than 2 Years of Age

Treatment of children with neglected DDH presenting after 2 years of age can be challenging. Many of these children require open reduction along with femoral shortening osteotomy to reduce the hip and additional concomitant or delayed acetabular procedures to achieve adequate coverage of the femoral head **(Fig. 5)**. As the age of the child increases, not only the complexity of the procedure
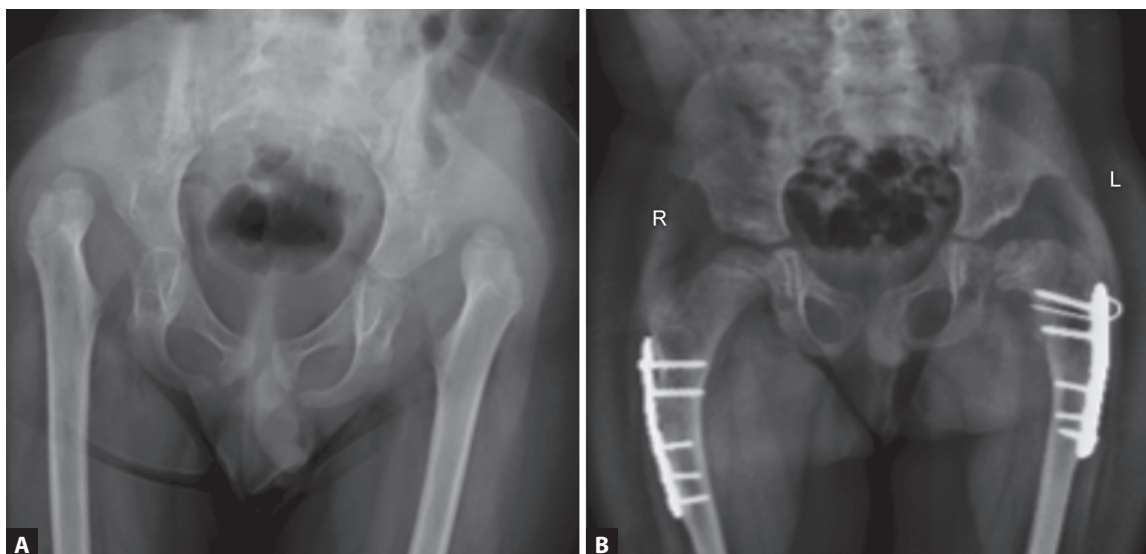
Figures 5A and B (A) Anteroposterior radiograph of the pelvis of a 5-year-old boy with bilateral neglected DDH showing B/L dislocated hips; (B) Postoperative X-ray following B/L open reduction, femoral shortening osteotomy and acetabuloplasty showing well contained hips on both sides

increases, but also the risk of complications often increase and the results become more unpredictable.

PREVENTION OF HIP DYSPLASIA

Early diagnosis is important for prevention of poor outcomes in DDH as early treatment by nonsurgical methods can decrease the risk of surgical intervention and its complications as such. Various screening programs are in practice across the world based the geographic incidence and also national health policies. Although routine ultrasound screening of all the newborn may potentially eliminate the disease burden, practically this may not be possible in all healthcare settings because of limited resources.

Simple detailed screening by routine hip examination of all newborns should be performed and will go a long way in decreasing the disease burden in a country like India. An important aspect of successful clinical diagnosis is that clinicians must be properly trained and skilled in performance of the tests for neonatal hip instability. The goal of prevention is to essentially eliminate the possibility of an unstable hip in an older child and this goal may be reasonable with early examination in all children in our system.

MORE ON THIS TOPIC

American Academy of Orthopedic Surgeons. Detection and non-operative management of pediatric developmental dysplasia of the hip in infants up to 6 months of age. Available from: http://www.aaos.org/Research/guidelines/DDHSummaryofRecommendations.pdf. Accessed Sep 28, 2014.

Herring JA, Sucato DJ. Developmental Dysplasia of Hip. Herring JA, ed. Tachdjian's Pediatric Orthopedics. 4th ed. PA: Elsevier; 2011. pp. 637-770.

Price CT, Ramo BA. Prevention of hip dysplasia in children and adults. Orthop Clin N Am. 2012;43:269-79.

Weinstein S. Developmental Hip Dislocation and Dysplasia. PA:Wolters Kluwer. 2012.

Weinstein SL. Developmental hip: Dysplasia and dislocation, Chapter 24, Lovell and Winter's Pediatric Orthopedics. 7th ed. Philadelphia: Lippincott Williams and Wilkins. 2013. pp. 988-1038.

IN A NUTSHELL

1. The American Academy of Pediatrics defines developmental dysplasia of the hip as a condition in which the femoral head has an abnormal relationship to the acetabulum.
2. DDH is therefore a wide spectrum that includes mildly shallow acetabulum (acetabular deficiency only) with a well-located femoral head at one end, to subluxation (partial loss of contact between the articular surfaces), or frank dislocation (complete loss of contact between the articular surfaces) at the other end.
3. Reported risk factors for DDH include breech presentation, female gender, positive family history, torticollis, metatarsus adductus, oligohydramnios, and hip asymmetry. Some of these enumerated factors lack robust evidence, but are pointers towards good clinical examination in this population.
4. Clinical examination remains the gold standard for diagnosis of unstable DDH. Investigations are merely supportive. Stable DDH is purely a radiographic or imaging diagnosis.
5. The primary aim of management of unstable DDH is to achieve a stable and concentric reduction as early as possible.

Chapter 49.7
Legg-Calvé-Perthes Disease
Venkatadass K, Harish S Hosalkar

Legg-Calvé-Perthes disease (LCPD) involves sectoral or occasionally global avascular necrosis of the capital femoral epiphysis due to temporary interruption of the blood supply to the bony nucleus of the proximal femoral epiphysis. There are changes in the capital femoral epiphysis and metaphysis, growth plate, and the acetabulum (primary or secondary). The necrotic bone of the epiphysis is gradually replaced by new bone and over 2–4 years healing of the epiphysis usually occurs. In the early stages of the disease, the epiphysis may extrude outside the confines of the acetabulum and this may predispose to femoral head deformation and articular incongruity.

EPIDEMIOLOGY

The LCPD usually affects children between 2 years and 14 years of age. The peak age of onset in western countries is around 5 years whereas it is around 7 years in Indian children. The male to female ratio is about 5:1. There is marked geographic variation in the frequency of the disease. It has been reported that even within India, the incidence in Vellore (south-east) is 0.4 per 100,000 per annum for 0–14 years olds whereas in Manipal (south-west) it is 4.4 per 100,000 per annum in children from 0–14 years. The condition tends to be bilateral in about 10% of children. The differential diagnosis for simultaneous bilateral hip osteonecrosis includes conditions such as Meyer dysplasia, spondyloepiphyseal dysplasia, multiple epiphyseal dysplasia, sickle cell disease, Gaucher disease and hypothyroidism.

ETIOPATHOGENESIS

The exact etiology of this 100-year-old disease still remains elusive. It appears to be a multifactorial disease caused by a combination of genetic and environmental factors. According to this view, genetic factors impart *susceptibility* to the disruption of the blood supply to the femoral head, whereas environmental factors, such as repeated subclinical trauma or mechanical overloading related to hyperactivity of the child, trigger the disease. Other etiologies that have been proposed include: collagen mutation or hereditary factors, hyperactivity with subclinical trauma to the femoral head vascularity, insulin-like growth factor-1 pathway abnormality, coagulopathy/thrombophilia, vasculopathy, inflammatory process, venous congestion, arterial occlusion, and maternal or passive smoking.

Disruption of the blood supply to the femoral head is the key pathogenic event that initiates disease process. It is debatable whether a single episode or multiple episodes of ischemia are necessary to produce the disease. The pathogenesis of femoral head deformity in the immature femoral head is complex. From a mechanical perspective, the infarcted femoral head begins to deform when the forces applied to the femoral head due to loading are greater than its ability to resist deformation **(Fig. 1)**.

An experimental study in a piglet model by ligating the femoral neck blood vessels has elucidated the temporal evolution of histopathological changes. Along with the necrosis of the bony epiphysis, cell death is observed in the deep layer of the articular cartilage, which has blood supply from the subchondral bone. This layer serves as the secondary center of ossification and change in the shape of femoral head (coxa irregularis) is often due to asymmetric restoration of growth of this layer. In addition
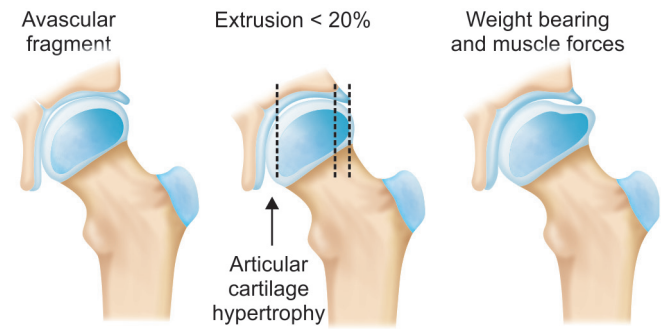
Figure 1 Pathogenesis of femoral head deformation

to this, the potential disturbance to the metaphyseal physis leads to changes in the alignment and length of the femoral neck (coxa breva, coxa vara or coxa valga). Primary or secondary involvement of the acetabulum in terms of dysplasia or retroversion has also been noted in several cases.

CLINICAL PRESENTATION

The most common presenting symptom is a painless limp of varying duration. The patient may report intermittent hip, thigh or even knee pain that is typically not severe and may not necessitate use of a crutch. Less commonly, the onset of the disease may be much more acute and may be associated with a failure to ambulate. Parents often attribute these symptoms to a traumatic event.

Usually, the child walks with a Trendelenburg gait; however, antalgic gait may be particularly prominent after strenuous activity at the end of the day. Hip motion, primarily internal rotation and abduction, is limited. Early in the course of the disease, the limited abduction is secondary to synovitis and muscle spasm, whereas in the later stages with the deformation of the head there may be a mechanical block limiting abduction. Wasting of gluteal and thigh muscles and limb length discrepancy are findings in the later stages of the disease. The classic phenotype of a child with LCPD is a small, thin, fairly active child often involved in sporting activities.

IMAGING

A plain radiograph of the pelvis in anteroposterior and frog leg lateral projections forms the primary imaging tool in assessment of the LCPD hip. It is used to diagnose, stage, provide prognosis, follow the course of the disease, and assess results. The earliest plain radiographic finding is an apparent increase in the medial joint space followed by an increased density of the capital femoral epiphysis. Because radiographic changes may not be apparent for almost 3–6 months after the onset of the disease, bone scan and MRI have been investigated to provide an earlier diagnosis, but their clinical value is not clearly established yet. Gadolinium enhanced MRI is as good as bone scan in providing early diagnosis with the advantage of being a nonionic investigation involving no radiation. There is some role of dynamic vascular flow MR imaging being a good diagnostic and prognostic predictor although it is far from being used as an universal tool.

Radiographic Classifications

Catterall Groups I, II, III and IV (based on radiological assessment of hip) represent 25%, 50%, 75% and total head involvement, respectively. Catterall also described the head-at-risk signs associated with poor outcome. These include presence of a horizontal growth plate, a radiolucent defect between the lateral epiphysis and metaphysis (Gage's sign), metaphyseal cysts, lateral calcification, or a lateral subluxation.

Due to the poor interobserver reliability of Catterall classification, Salter and Thompson reduced the classification to two groups, involving less than half or more than half or of the bony epiphysis undergoing necrosis. Herring's lateral pillar classification is based on the height of the lateral pillar, defined as the lateral 15–30% of the epiphysis on the anteroposterior radiograph. Group A represents no loss of the lateral pillar height, group B represents less than 50% loss and group C represents more than 50% loss of the lateral pillar height.

Both Catterall and Herring classifications can be applied only at the stage of maximal fragmentation and cannot be applied in the early stages prior to the development of femoral head deformity. The *modified Elizabeth Town classification* by Joseph et al. can be applied at the early stages of the disease and as well helps in deciding on the management. The classification is based on the natural history of the disease in four stages and the first three stages are divided into early and late based on the radiographs **(Box 1 and Fig. 2)**.

NATURAL HISTORY

The LCPD is a self-limiting disorder and complete revascularization of the epiphysis is usually noted in children less than 12 years.

Avascular necrosis triggers synovitis, articular cartilage hypertrophy and hypertrophy of ligamentum teres, which along with muscle spasm can lead to extrusion of femoral head. Weight bearing stress on the necrotic, soft femoral head across the acetabular margin leads to deformity of the head. More than 20% of extrusion is a high-risk factor for irreversible head deformation.

It was noted that in untreated children, femoral head extrusion abruptly increased as they reached the stage of late fragmentation. Hence, the stage of late fragmentation (Stage IIb) divides the cycle

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BOX 1 Modified Elizabeth Town classification for Perthes disease

Stage I: Stage of avascular necrosis
      Ia: Sclerosis of capital femoral epiphysis
      Ib: Sclerosis and collapse of capital femoral epiphysis
Stage II: Stage of fragmentation
      IIa: Early fragmentation—one or two fissures seen
      IIb: Late fragmentation—more than two fissures
Stage III: Stage of reconstitution
      IIIa: New bone formation limited to lateral 1/3 of epiphysis
      IIIb: New bone formation more than 1/3 of epiphysis
Stage IV: Healed stage
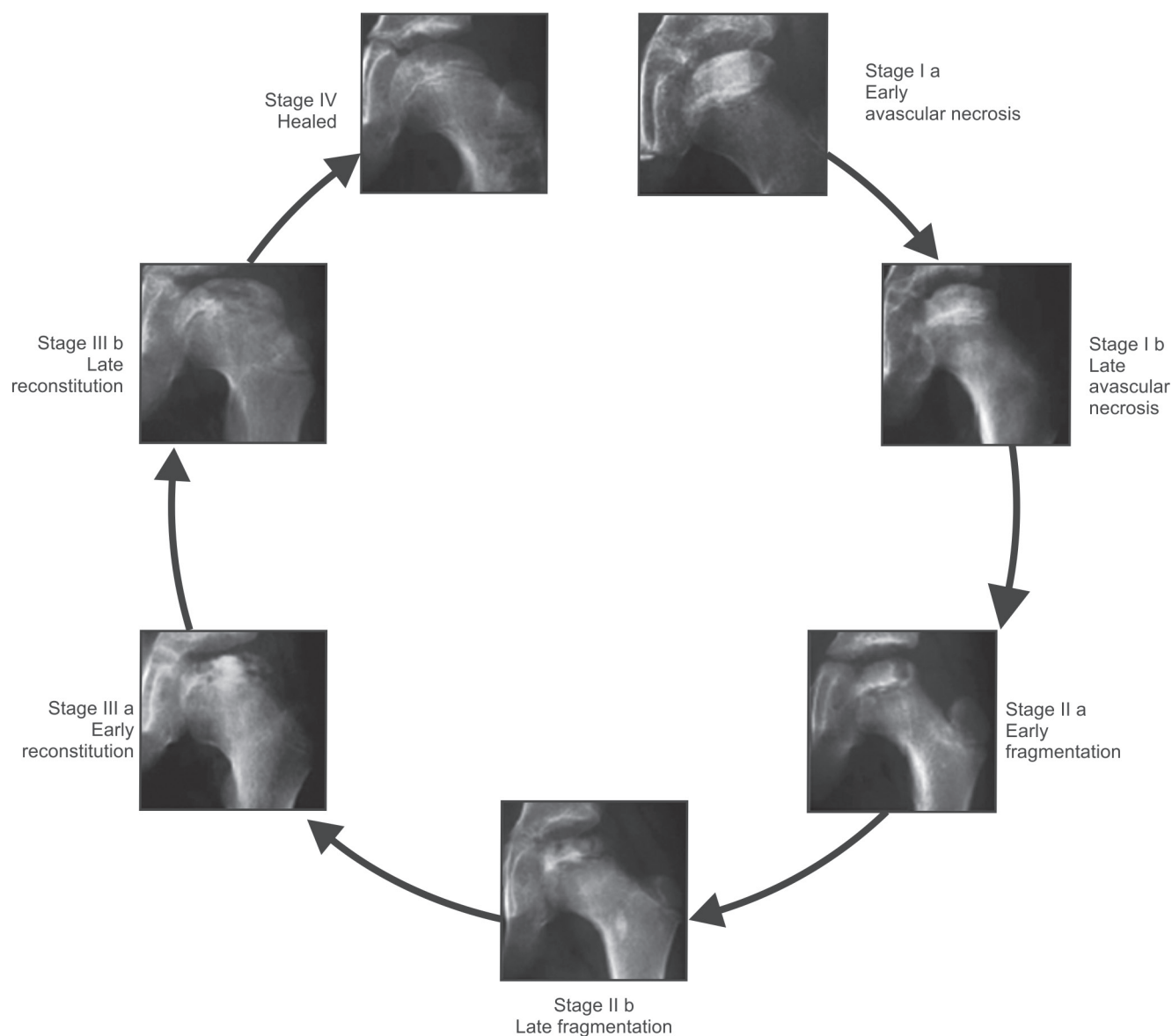
Figure 2 Stages of evolution of Perthes disease as described by Joseph et al.

of evolution into two distinct parts—one prior to this stage and the other after this stage. But naturally, any intervention to prevent femoral head deformation is likely to succeed when instituted prior to this stage. Any intervention thereafter is either remedial in nature or a salvage.

TREATMENT

The goal of treatment is to achieve a spherical, well-covered, concentric femoral head with hip range of motion that is close to normal and to postpone the pathway towards early arthritis of the joint. The nature of treatment depends on the stage of the disease and age of the child at presentation. All patients presenting before Stage IIb may be offered containment to minimize or prevent head deformation as much as possible. Containment is the term used to describe any intervention, which positions the anterolateral part of the femoral epiphysis inside the acetabulum, thereby protecting it from deforming forces. Containment can be achieved by two different methods. The first involves positioning the femur either in abduction and internal rotation or abduction and flexion, by casting, bracing or surgery on the femur. Alternatively, containment can be achieved by a reorienting osteotomy on the pelvis (Salter/Triple Innominate Osteotomy). In today's world many nonsurgical methods of containment are less popular due to issues of comfort and compliance. **Table 1** outlines the decision making in early stages of Perthes disease.

Treatment in Late Stages

For children presenting after late fragmentation, the head deformity has already occurred and the treatment option needs to be tailored to each patient depending on the type of deformity, range of motion, congruency of the hip and issues of intra- and extra-articular impingement. Various reconstructive procedures

including valgus osteotomy, shelf procedures, femoral head neck osteochondroplasty, relative neck lengthening, femoral head reduction with or without a peri-acetabular osteotomy and labral repair are done to restore the anatomy to as normal as possible with the aim of delaying secondary osteoarthritis.

Future Directions

Experimental studies in animal models have given a better understanding of the pathogenesis of LCPD and role of various inflammatory markers are being studied. Anabolic strategy helping in bone formation using agents like BMP-2, anticatabolic strategies using local bisphosphonates and combination therapies are being studied in animal models and this century old mystery disease may be amenable for pharmaceutical or biologic intervention in the future.

IN A NUTSHELL

1. Legg-Calvé-Perthes disease (LCPD) refers to partial or complete avascular necrosis of the capital femoral epiphysis due to temporary interruption of the blood supply. The exact etiology of LCPD disease is still not known.
2. Late onset LCPD (at about 7 years) is more prevalent in India. The most common presenting symptom is a painless limp of varying duration.
3. Radiographic changes may not be apparent for almost 3–6 months after the onset of the disease; the earliest finding is an apparent increase in the medial joint space followed by an increased density of the capital femoral epiphysis.
4. Utility of bone scan and MRI is not clearly established.
5. The containment procedures are aimed at preventing the deformation of head and are best done before the stage of late fragmentation.
6. Children presenting at later stages may require complex reconstructive surgeries to help re-establish the anatomy and function of the hip, as much as possible.

MORE ON THIS TOPIC

Choi IH, Yoo WJ, Cho TJ, Moon HJ. Principles of treatment in late stages of Perthes disease. Orthop Clin North Am. 2011;42:341-8.

Hosalkar HS, Mulpuri K. Legg-Calve-Perthes disease: Where do we stand after 100 years. Clin Orthop Rel Res. 2012;470.

Joseph B, Price CT. Principles of containment treatment aimed at preventing femoral head deformation in Perthes disease. Orthop Clin North Am. 2011;42:317-27

Joseph B. Prognostic factors and outcome measures in Perthes disease. Orthop Clin North Am. 2011;42:303-15.

Little DG, Kim HW. Future biologic treatments for Perthes disease. Orthop Clin N Am. 2011;42:423-7.

Perry DC, Hall AJ. The epidemiology and etiology of Perthes disease. Orthop Clin N Am. 2011;42;279-83.

Wenger DR, Hosalkar HS. Principles of treating the sequelae of Perthes disease. Orthop Clin North Am. 2011;42:365-72.

Table 1 Treatment of Legg-Calvè-Perthes disease

Age at onset	Extrusion of femoral head	Range of motion	Recommended treatment
Under 8 years	Absent	Good	• No containment • Preserve range of motion • Monitor for extrusion with radiographs every 4 months
	Present	Good	• Contain as soon as possible
		Poor	• Restore motion by traction/abduction cast for 6 weeks • Treat by containment once motion is restored
8 years and older	Present or Absent	Good	• Contain as soon as possible
		Poor	• Restore motion by traction/abduction cast for 6 weeks • Treat by containment once motion is restored

Chapter 49.8
Osgood-Schlatter Disease
Joana Manuel Ferreira Freitas, Harish S Hosalkar

Osteochondrosis of the tibial tubercle is recognized as a traction apophysitis and is therefore an inflammatory condition. It is characteristically presents with pain in the anterior tibial tubercle with activities that typically include running, jumping, kneeling or squatting. It is caused by tensile forces of the patellar tendon on the anterior tibial tubercle typically in a growing skeleton and hence is common during final stages of growth spurt. The diagnosis is usually based on a typical history and physical examination.

EPIDEMIOLOGY

The condition occurs in about 21% of young athletes, and 4–4.5% in young non-athletes. It occurs bilaterally in 20–30% of the cases. Traditionally, boys used to be more affected than girls, with a peak incidence in adolescence. Currently, with the increase in sporting activity for girls, the incidence is similar, presenting an earlier peak for girls between 10–13 years. It is more prevalent in activities as running, basketball or hockey and skates for boys; and gymnastics, volleyball and skating in girls.

Two conditions seem to be fundamental to the pathomechanism of this apophysitis—rapid growth in an adolescent who is usually active in sports where the skeletal growth and muscle lengthening usually have a mismatch and open apophysis with open growth plates (essentially demonstrating skeletal immaturity).

ETIOLOGY

The main causes postulated are repetitive microtrauma and constant traction forces within the patellar tendon in its insertion to the tibial tuberosity—causing an apophysitis or overuse syndrome. This constant stress on the anchor point (which is less resistant than normal tendon anchor in the adult bone) is postulated to lead to microfractures that can contribute to the local pain.

Anatomy and Development

Four stages are described in the development of the tibial tuberosity: (1) *Cartilage*—occurs before the appearance of secondary ossification nucleus usually between 8 and 10 years of age; (2) *Apophysis*—when one or more ossification centers are already evident in the tibial tuberosity, usually occurs earlier in girls than in boys; (3) *Epiphyseal*—usually occurs around the time when the two ossification centers of the proximal tibia and the tibial tuberosity join; (4) *Bone*—corresponds to the permanent closure of the physis of the tuberosity, in girls usually around 15 years of age and in boys at 17 years of age.

PATHOGENESIS

There are three histologic areas currently identified in the tibial tuberosity: (1) *Proximal zone*—columnar cartilage is identical to the proximal physis of the tibia; (2) *Intermediate zone*—with fibrocartilage; and (3) *Distal zone*—zone of fibrocartilage transition to the tibial perichondrium. Because of this histological appearance, growth and maturation tends to occur from proximal to distal, similar to the closure of the physis. Weak link is therefore located in the anchorage point of the patellar tendon, on the anterior aspect of the tibial tuberosity, corresponding to area of new bone formation in front of the secondary ossification center. Conversely, in avulsion fractures of the tibial tuberosity, 1 weak spot is located on the rear segment of this tuberosity.

Hirano and colleagues described five stages based on their findings (ref): (1) *Normal*—there are only minor complaints of pain, no swelling or effusion, no changes in MRI; (2) *Initial stage*—MRI shows or decreased signal intensity in the center of the secondary ossification; (3) *Progressive stage*—there is a lesion of the secondary center of ossification, and cartilage damage at the tibial tuberosity; (4) *Terminal stage*—resolution of edema and no signs of healing; (5) *Final stage*—prominence of the tibial tubercle, with normal imaging appearance. Although described, these stages are not routinely used in assessing, documenting and treating this condition in the current standard of care.

The imaging studies (MRI, bone scintigraphy, and CT scan) have supported the notion that local inflammation of soft tissues plays a notable role in the pathology and its clinical manifestations, more than the bone involvement.

CLINICAL FEATURES

The diagnosis is primarily based on clinical history and supportive physical examination findings including: pain localized to the tibial tuberosity, with or without swelling that is palpable and visible **(Figs 1A and B)**, related directly to the physical activities. Tightness of mostly all major groups of long lower extremity muscles, particularly rectus femoris, IT band and hamstrings. Soft tissue inflammation may sometimes be associated with a local bursitis. In chronic conditions, there are irregularities noted during palpation of bony prominences, when fragmentation of the physis occurs.

Younger children may have an antalgic gait with typical flexed knee posture. Effusion is not a typical finding.

DIAGNOSIS

Although it is a clinical diagnosis, it is good practice to obtain plain radiographs to identify and rule out any other pathology like bone cysts or tumors that may rarely present in this age group. X-rays also help to ascertain correct mechanical axis and confirm appropriate joint space and patellofemoral relationship. Radiographs may demonstrate some protrusion of the anterior tibial tuberosity. It may be associated with fragmentation at the physis **(Fig. 2)**.

MRI or advanced imaging like CT is useful when there is suspicion of tumor lesions or when the pain is more severe than usual, or there is significant soft tissue edema, to characterize the pathology further.

Differential Diagnoses

Avulsion fracture of the tibial tuberosity **(Fig. 3)**, tumors, Larsen-Johansson syndrome, patellofemoral stress, infections or bursitis need to be differentiated. All these entities can cause pain at the
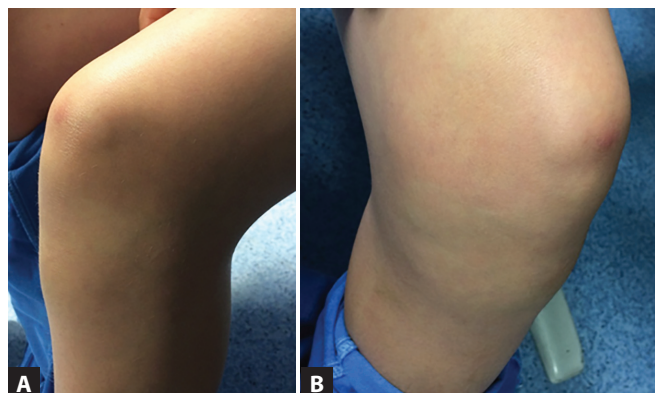
Figures 1A and B Clinical image of an Osgood Schlatter disease. (A) Note the bump in the tibial tuberosity; (B) From a different perspective, the prominence of the tibial tuberosity can also be noted

Figure 2 Radiological image of an Osgood-Schlatter disease. Note the discrete fragmentation of the tibial tuberosity

Figure 3 Radiological image on a tibial tuberosity fracture. We can differentiate it from Osgood-Schlatter disease as there is an avulsion instead of a fragmentation as shown in Figure 2

level of the tibial tuberosity, with palpable prominence and pain related with physical activities in this age group.

MANAGEMENT

The avoidance of strenuous activities that aggravate the problem is usually effective in controlling the symptoms. Resting and avoidance of PE activities in school for about 3 weeks usually allows symptoms to subside followed by stretching therapy for all the major groups of muscles in the lower extremity. These should focus on quadriceps, but also include IT band, hamstrings, gastrocnemius and core muscle groups. Anti-inflammatory medications may help and opioids are rarely necessary. Ice and/or cryotherapy may offer benefit in select cases. Best advice to these adolescents is to *slow down* for the 3–6 weeks during treatment and rehabilitation for resolution of symptoms. Splinting or casting

is rarely indicated in our experience. Braces to offload the patellar tendon are available and can be tried in resistant cases.

Surgery is requited in less than 1% of cases and conservative treatment should be patiently encouraged. Chronic cases can have symptoms for more than 12–18 months in some cases. Surgery, if at all required, involves excision of bone ossicles or fragmented pieces of the tuberosity with osteoplasty or osteochondroplasty (surgical success rate about 90%), or regulation of the anterior tibial prominence (surgical success rate about 85%). As far as possible, these should be offered after skeletal maturity to avoid any growth related issues.

OUTCOME

Most, if not all patients, have a good prognosis and the symptoms eventually resolve spontaneously. Rarely, patients may have knee issues in adulthood.

IN A NUTSHELL

1. Osgood-Schlatter disease refers to traction apophysitis or inflammatory osteochondrosis of tibial tubercle, presenting as pain in the anterior tibial tubercle or anterior knee pain usually in skeletally immature adolescents.
2. The main cause proposed is repetitive microtrauma, and constant traction within the patellar tendon and/or its insertion at the tibial tuberosity.
3. Growth spurt with bone-muscle length mismatch and skeletal immaturity with open physis are thought to be two important key determinants.
4. Avulsion fracture of the tibial tuberosity can be a differential diagnosis but may not be directly related, although some correlation has been reported.
5. Rest from excess sports and avoidance of provocative activities usually are effective in controlling the symptoms.
6. Surgical intervention is extremely rare. Excision of bone fragments or osteoplasty of the anterior tibial prominence may be indicated in cases of chronic symptoms beyond skeletal maturity.
7. It has good prognosis, most of the cases resolve spontaneously with skeletal maturity, physiotherapy modalities and continued stretching.

MORE ON THIS TOPIC

Frey S, Hosalkar H, Cameron DB, et al. Tibial tuberosity fractures in adolescents. J Child Orthop. 2008;2:469-74.

Ganley T, Kolze E, Gregg J. Pediatric sports medicine: Osgood-Schlatter disease. In: Dormans JP. Pediatric Orthopaedics. Core Knowledge in Orthopaedics. 1st ed. Philadelphia, Pennsylvania: Elsevier Mosby; 2005. p. 141.

Hunt D, Macnicol M. Distinct cause of anterior knee pain: Osgood-Schlatter condition. In: Benson M, Fixsen J, Macnicol M, Parsch K. Children's Orthopaedics and Fractures. 3rd ed. London: Springer-Verlag; 2010. p. 497.

Moutzouros V, Parker R. Osteochondroses: Osgood-Schlatter disease. In: DeLee J, Drez D, Miller M. Orthopaedics Sports Medicine, Principles and Practice. 3rd ed. Saunders Elsevier: 2009. pp. 1526-1529

Price C, Herrera-Soto J. Extra-articular injuries of the knee: Avulsion of the tibial tuberosity. In: Beaty J, Kasser J, Flynn J, et al. Rockwood and Wilkins' Fractures in Children. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. pp. 870-75.

Skinner H, Fitzpa trick M. Pediatric problems: Osgood-Schlatter disease. In: Skinner H, Fitzpa trick M. Current Essentials Orthopedics. 4th ed. USA: McGraw Hill Companies; 2008. p. 231.

Chapter 49.9
Congenital Talipes Equinovarus
Mandar V Agashe, Harish S Hosalkar

Congenital clubfoot (congenital talipes equinovarus [CTEV]) is a complex congenital anomaly of the lower extremity mainly involving the foot and comprising of four main components:
1. Equinus in ankle,
2. Varus in hindfoot,
3. Adductus in the forefoot, and
4. Cavus of the foot.

EPIDEMIOLOGY

The reported incidence of congenital clubfoot is around 1:1,000 live births though this incidence varies in various populations. The incidence is reported to be highest in western population especially African-Americans and the lowest in Eastern Asian countries like Japan and Korea. Though exact population studies are not available for the Indian population, the incidence of congenital clubfoot in India seems to be somewhere in the middle of these two extremes. The problem of clubfoot, especially neglected clubfoot has become quite relevant in India so much so that the Government of India has made congenital clubfoot one of the seven notifiable congenital anomalies in 2012.

This condition is much more common in boys with a reported male to female ratio of about 2:1. There is also greater incidence of clubfoot in families of affected individuals. The chance of a child having clubfoot is about 2.9%, if a first degree relative is affected and is as high as 33% in twins.

ETIOLOGY

Two main theories have been put forth for the etiology of congenital clubfoot—genetic and environmental. The genetic component is polygenic, i.e., the defect is carried not just by a single gene but by multiple genes. Recent reports however have reported a single gene to carry the genetic component with a penetrance of around 33%. Family studies have proved this genetic component to be very important though we are still a long way from exactly isolating a particular gene that is responsible for all cases of congenital clubfoot.

The proponents of the *environmental theory* cite the embryological causation of congenital clubfoot. In utero, the fetus remains in a *physiological clubfoot* state till about the 11th week, with varus of the heel, adductus of the forefoot and equinus. During that period, the leg is in the *fibular phase*, i.e., in which the fibula and the fibular sided structures grow faster than the medial or tibial sided ones. This can explain the clubfoot-like appearance of the foot. Only after about the 11 week of life, does the tibial side grow and the foot assumes a normal appearance. Clubfoot has been experimentally induced in animals by introducing environmental toxins at a stage corresponding to the 9th week of pregnancy in humans. Clubfoot has also been seen to be more commonly found in babies born to mothers who smoke.

A third relatively infrequently cited theory is that of *intrauterine crowding*. Though logical, this theory does not have many proponents, since clubfoot has not been known to be more common in conditions that have intrauterine crowding like twins, oligohydramnios, etc. Also, with the help of prenatal ultrasound, it is clearly seen that the fetus moves the feet almost constantly, hence, it is very unlikely that the fetus will assume a fixed abnormal posture over time.

PATHOGENESIS

There has been a lot of controversy about the primary pathological structure in congenital clubfoot. With the help of detailed electron microscopic studies, the primary pathological cells in the pathogenesis of congenital clubfoot have been described to be modified myofibroblasts which form bundles of wavy collagen fibers which are known as *crimp*. These crimp fibers have significant elastic recoil which form the basis of the serial correction technique which is widely followed almost all over the world.

As a result of these fibers, the secondary and tertiary effects are seen in the ligaments, muscles and bones. The ligaments and soft tissues on the posterior, medial and plantar aspect of the foot and ankle are shortened and contracted. The ligaments most commonly shortened are the posterior talocalcaneal ligament, calcaneofibular ligament, the short and long plantar ligament, the spring ligament and the fibro-fatty tissue at the junction of the flexor hallucis longus and the flexor digitorum longus (more popularly known as the *Knot of Henry*). The muscles that are contracted are the tendo-achilles, the tibialis posterior, the long and short flexors of the toes, and the small muscles on the plantar surface of the foot while the peronei are stretched out and weakened. The bones are also notably affected the major brunt being borne by the talus. The anterior portion of the talus (i.e., the talar neck) is deviated medially and plantar-wards, and the whole talus is shortened and ossification is delayed. The other bones, i.e., calcaneum, navicular and the metatarsals are more or less similarly involved with marked medial displacement and shortening on the medial side.

CLINICAL FEATURES

The clinical features of congenital clubfoot are quite striking and obvious even at birth **(Figs 1A and B)**. There is inward and downward turning of the entire foot with the forefoot in adductus (turning towards the midline), heel in varus and a presence of the cavus foot deformity. This cavus deformity is manifested by the presence of a very deep medial crease as well as the pronation of the first two rays in comparison to the lateral three toes. The talar head is very prominent on the lateral aspect and the navicular is medially displaced—sometimes so much that it is almost in contact with the medial malleolus. There is usually a deep crease in the posterior aspect of the heel and the heel feels *empty*, i.e., since the calcaneum is in severe equines (plantar flexion), the calcaneum is not easily palpable in the pulp of the heel. The tendo-achilles is always tight. The calf muscles are quite atrophied and this atrophy can be quite marked even at birth in severe unilateral cases. There may be internal tibial torsion in varying amounts and in occasional cases there may be involvement of the knee joint and femur in some form or other.

In case of neglected clubfeet, these deformities, which are relatively supple early on in life, become rigid and fixed. The child will then start to walk on the lateral border of the foot with resultant callosities on the lateral border of the foot with possible skin breakdown. The atrophy of the calf muscles as well as the internal tibial torsion also becomes marked and there will be notable limb length discrepancy over time.

It is also important to examine the other parts of the body as well as other joints to rule out other secondary types of clubfoot. Neuromuscular clubfoot has to be ruled out by examination of the spine to look for any signs of spina bifida like a tuft of hair, lipofibroma in the midline as well as a palpable defect in the posterior element of the spine. Arthrogryposis multiplex congenita is an important cause of secondary or nonidiopathic clubfoot and hence range of motion as well as deformities of other joints have to be seen and looked for **(Fig. 2)**. Hips and knees are the most common joints involved after clubfoot in arthrogryposis.

DIAGNOSIS

The diagnosis of congenital clubfoot is evident on clinical examination and as such no further investigations are necessary for the diagnosis. In neglected clubfeet, plain radiographs of the
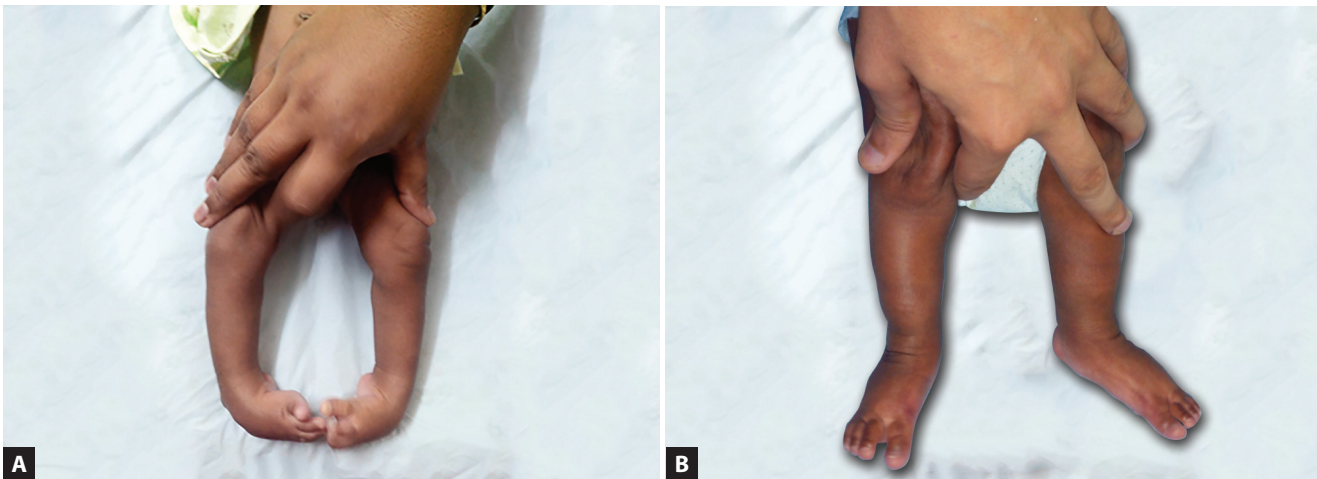
Figures 1A and B (A) Clinical photograph of a 15-day-old child with bilateral severe clubfeet showing the typical deformities of cavus, forefoot adduction, heel varus and equinus; (B) Clinical photograph of the same child after 4 Ponseti serial plasters and percutaneous tendo-achilles tenotomy showing excellent correction and almost normal looking feet

feet—anteroposterior and lateral views may be of benefit for documenting the severity of involvement and planning of surgery.

Differential Diagnosis

A classical congenital clubfoot remains a clinical diagnosis. *Postural clubfoot* is an important differential diagnosis of very mild clubfoot and is a very flexible form of clubfoot. It can be differentiated from idiopathic clubfoot by the ability to completely correct the foot at diagnosis. The other differential for idiopathic clubfoot is *congenital metatarsus adductus*. Congenital metatarsus adductus is basically only the inward turning of the foot at the level of the forefoot and the midfoot, without any hindfoot equinus. This has a relatively benign course and is usually treated only by maternal manipulation and rarely requires further treatment in the form of casting.

CLASSIFICATION

Two main classification systems exist for gradation of severity in congenital clubfoot including the *Pirani classification* and the *Dimeglio classification*. Dimeglio classification was first described in 1995 and grades clubfoot with the help of four different deformities, i.e., adductus of the forefoot, varus of the heel,

Figure 2 Clinical photograph of a 1-month-old child with arthrogryposis multiplex congenita with bilateral severe clubfeet, knee deformities as well wrist deformities. The child also shows absence of skin creases typically known as puppet doll appearance

equinus of the ankle and rotation. Accordingly every clubfoot can be classified into any one of the four categories:

1. *Grade 1* Benign or *soft* clubfoot which is readily reducible by digital pressure and is almost similar to a postural clubfoot.
2. *Grade 2* Moderate clubfoot—reducible with a moderate degree of resistance.
3. *Grade 3* Severe clubfoot—only reducible partially against strong resistance.
4. *Grade 4* Very severe clubfoot—not reducible even against strong resistance.

Though interobserver studies have shown the Dimeglio classification to be the most reliable, it is not very commonly used in clinical practice since it is difficult to use as a means of monitoring and guiding treatment. As against that, the more recent *Pirani classification* is a much simpler method and can be used effectively for monitoring the progress of treatment especially by the Ponseti method. The Pirani score is a score with six points of reference—three in the hindfoot (rigid equinus, posterior crease and empty heel) and three in the midfoot (talar head, lateral border and medial crease), with 1 point each for a severe deformity, 0.5 point for a mild deformity and 0 point for an absent deformity. Thus, every foot will be graded from 0 to 6 with six being the most severe. Since the score is a numerical value, it is easy to exactly quantify the progress of the treatment over several weeks.

TREATMENT

Moritz was reportedly the earliest to treat congenital clubfoot surgically and he described the procedure of open lengthening of the tendo-achilles for untreated clubfoot. It was Kite who reportedly first described the method of casting though most of the patients treated with Kites method of serial casting used to land up with surgery. Turco in his elegant treatise on congenital clubfoot described in detail the surgical correction of clubfoot which is popularly known as *posteromedial soft tissue release (PMSTR)* or simply PMR. Though effective, this method has been questioned due to many issues related to the scarring of the soft tissues of the foot, which, on many occasions result in a stiff, painful foot. Popularity of this method gradually decreased over the years and it is now reserved for severe recalcitrant neglected clubfeet.

Ponseti Method of Serial Casting

This is currently the most widely used method in treatment of clubfoot. The Ponseti method is not just a method of serial casting but it can be rightly summed up as a:

- Specific method of manipulation to achieve correction;
- Specific method of casting to maintain correction;
- Specific method of bracing to prevent relapses; and
- Specific method of treating relapses.

The treatment is to be started soon after birth, many a time even in the neonatal intensive care unit (NICU) set-up in order to gain the maximum benefit of the maternal hormone relaxin for stretching of soft-tissues. Neonatologists may consider referring a case of suspected congenital clubfoot to a trained pediatric orthopedic surgeon as soon as possible after birth to start serial casting in the best interest of good patient outcomes. The treatment starts with manipulation of the foot in a specific manner followed by above knee plaster cast application with the knees flexed 90°. In this method, all deformities are attempted to be corrected simultaneously with the fulcrum of manipulation to be the talar head (unlike the Kites method where the fulcrum is the calcaneocuboid joint). Usually between 4 and 8 serial weekly casts may be required to achieve correction of all the deformities except equinus. Equinus deformity usually cannot be treated only with serial casting and requires a small percutaneous tendo-achilles tenotomy, which can be done in the clinic under local anesthesia. Once the foot is fully corrected, another above-knee cast is given which is kept for a period of around 3 weeks, after which the casting phase is complete and the child goes to the bracing phase.

The Bracing Phase
Bracing is an equally important component of the Ponseti method. The brace which is used in the Ponseti method is known as *Steenbeck splint*. It consists of a closed-box, high top shoe, with no medial wedge, connected to a bar, the width of the patient's shoulder, and attached at an angle of 70° for the affected foot and 45° for the nonaffected foot in case of unilateral clubfoot. This shoe has to be worn full time (i.e., around 23 hours a day) for a period of about 3 months after which the same brace is to be used till about 3 years of age mainly at night time and nap time. Compliance to bracing is the most important factor in preventing recurrences with some studies showing an odds ratio of almost 16 implicating noncompliance to bracing for causing recurrences.

Treatment of Recurrence
Treatment of recurrences in patients treated with Ponseti method is much simpler than in surgically treated patients. The specific component of recurrence has to be individualized and treated as such. Thus, a pure equinus recurrence can be treated with the help of a repeat tendo-achilles tenotomy. A mild generalized recurrence can be treated with repeat serial casting while recurrence of forefoot adduction and supination can be treated with a tibialis anterior tendon transfer to the lateral cuneiform. In case of severe recurrences, a PMR may be needed though this is a rarity.

Treatment of Syndromic and Neuromuscular Clubfeet
The Ponseti method can be also used for the treatment of syndromic, arthrogrypotic and neuromuscular clubfeet, though with less reliable outcomes. Serial casting can be attempted in syndromic and arthrogrypotic clubfeet with the clear understanding that more number of casts may be required than idiopathic clubfeet and a relatively low threshold should be kept for a surgical intervention like a PMR. In case of neuromuscular clubfeet like in spina bifida, it is relatively easy to achieve correction with casting but it is more difficult to maintain it even with bracing due to poor muscle tone and power. Hence, many a time repeat Ponseti casting may be required along with full formal surgery (PMR) for the same.

Treatment of Neglected Clubfoot
With the advent of better awareness about the conservative and nonsurgical treatment of clubfoot, the incidence of neglected clubfoot has thankfully decreased in the last few years. However, we still continue to get such cases especially in rural areas of the subcontinent. The management of neglected clubfoot requires specialized treatment and following methods can be used:

Soft tissue surgeries These include posterior release as well as posteromedial soft tissue release by the Turco or the Cincinnati method. Soft tissue surgeries alone can be used only in relatively younger patients till the age of around 4 years or so.

Lateral column shortening procedures These procedures like calcaneocuboid fusion or cuboid decancelation can be used either in isolation or in association with PMR in older children in the age group of around 4–7 years.

Bony fusion surgery These are reserved for quite older children with neglected severe clubfeet. The most common surgery in this group is triple fusion which includes fusion of the subtalar, calcaneocuboid and the talonavicular joint.

External fixators External fixators are excellent modalities of treatment for recalcitrant clubfeet. The most common fixator used worldwide is the Ilizarov external fixator which allows for gradual correction of the clubfoot deformity. However in India, the fixator designed by Professor BB Joshi known as the Joshi External Stabilization System (JESS) has become extremely popular due to its modularity, ease of application and use as well as limited cost as compared to the international brands.

IN A NUTSHELL

1. Congenital clubfoot is the most common congenital deformity in the lower limb requiring orthopedic management.
2. Congenital clubfoot has four main components—(1) Cavus, (2) Adductus of the forefoot, (3) Varus of the heel and (4) Equinus of the heel (remembered by the mnemonic CAVE).
3. Clubfoot is classified by two main classification systems—the Dimeglio and the Pirani classifications.
4. Syndromic and neuromuscular clubfoot are different entities and as such require early diagnosis and prompt and specialized treatment.
5. Treatment should begin as soon as possible, preferably in the first week of life itself.
6. The Ponseti method of serial casting is the gold standard in the management with very high success rate.
7. Bracing with the help of Steenbecks splint is very important in maintain correction and preventing recurrences.
8. It is sometimes necessary to use various types of surgeries judiciously in neglected clubfeet.

MORE ON THIS TOPIC

Bor N, Herzenberg JE, Frick SL. Ponseti management of clubfoot in older infants. Clin Orthop Relat Res. 2006;444:224-8.

Cooper DM, Dietz FR. Treatment of idiopathic clubfoot. A thirty year follow-up note. J Bone Joint Surg Am. 1995;77:1477-89.

Dobbs MB, Rudski JR, Purcell DB, et al. Factors predictive of outcome after use of the Ponseti method for the treatment of Idiopathic clubfoot. J Bone Joint Surg Am. 2004;86:22-7.

Gupta A, Singh S, Patel P, et al. Evaluation of utility of the Ponseti method of correction of clubfoot deformity in a developing nation. Int Orthop. 2008;32:75-9.

Morcuende JA, Dolan LA, Dietz FR, Ponseti IV. Radical reduction in the rate of extensive corrective surgery for clubfoot using Ponseti method. Pediatrics. 2004;113:376-80.

Ponseti IV. Congenital Clubfoot: principles of treatment. 1st ed. New York: Oxford University Press; 1996.

Chapter 49.10
Skeletal Dysplasias
Kuldeep Singh, Abhay Elhence

A child born with deformities of bones or having short stature (dwarf) is considered likely to be suffering from skeletal dysplasias or *dysostosis*. These are bone conditions consisting of a heterogenous group of disorders affecting the bone and cartilage and resulting in varied clinical presentations. Sometimes dysostosis and dysplasias are used interchangeably in labeling a child with bone defects. While dysplasias (Latin word meaning *bad growth*) are generalized bone abnormalities which are due to genetic defect in proteins or in regulation of bone formation, dysostoses on the other hand, are more localized and usually due to embryogenic development process.

NOMENCLATURE

Because of large number of bone disorders with overlapping clinical features, attempts were made to classify similar disorders into groups. It was also recognized that these disorders may be more complex than they appear to a physician. Hence, many attempts were made at classifying skeletal conditions and the first version of the *Nomenclature* was published in 1971. The clinical phenotype was used as the basis of classification as detail biochemical or molecular information was unavailable at that time. It was thought that the grouping might give a clue to causation by disturbances in related metabolic abnormalities (in the case of metabolic storage disorders). It also became imperative to classify disorders because of enormous number of conditions with nearly similar clinical features.

The current revision (published in 2011), as an outcome of skeletal dysplasia groups' meetings, includes an even larger number of dysplasias and is the most acceptable and widely used. For the last few revisions, systemic disorders with skeletal involvement have also being included like lysosomal storage disorders (*Group 27*), progeria syndromes with osteolysis (*Group 28*) and overgrowth syndromes (*Group 30*).

There were many criticisms to the classifications for being *hybrid* in nature, and being dissociated from other classifications systems. Another criticism for the nosology was the time gap between their meetings which is usually every 4 years. It is debated that with new information the nosology become outdated very fast. It was suggested by experts that we need to develop integration of nosology with ontology and semantics with cross-linking of the various databases. Such databases integration have already been initiated and researched on in form of *skeletome* project.

Advantages of Nosology
- Help clinician providing important diagnostic features
- Suggests the differential diagnoses to be considered
- Provides standards for comparison
- Act as a catalog of genes.

The summary of groups in recent *Nosology 2010* is summarized in **Table 1**.

APPROACH TO SKELETAL DYSPLASIA

As can be seen from earlier description of nomenclature and nosology for skeletal dysplasia, it is apparent that simple classification and guidelines cannot be applied in our day to day practice for accurate diagnosis of skeletal dysplasia given huge number of conditions with variety of presentations. Therefore, each child needs to be worked up in detail on an individual basis using, as far as possible, all available modalities toward the diagnosis.

The clinical features may provide the first clue towards diagnosis. There may be some subtle features on history and clinical examination. The approach usually applied toward short stature can be used for categorizing the patient with pathological disproportionate short stature as having skeletal dysplasia. However, it should be emphasized that certain skeletal dysplasia may not have short stature or may have subtle changes in skeletal system. The clinical features to look for in suspected skeletal dysplasias are summarized in **Table 2**.

A skeletal survey includes anteroposterior (AP), lateral and Towne views of the skull, AP and lateral views of the spine, and AP views of pelvis, extremities, hands, and feet. Other special radiograph may be obtained if needed. While evaluating them with a radiological skeletal survey, it has to be kept in mind that this should be prepubertal and preferably time framed to observe for changes with growth. Radiological classification is based on three step assessment for (1) disproportion, (2) ossifications of epiphyseal, metaphyseal and diaphyseal bone **(Figs 1A to C)** and (3) differentiation of normal variants from pathological abnormalities. Osteosclerotic disorders like osteopetrosis can be easily diagnosed with bone radiodensity **(Fig. 1D)**. Fractures may indicate osteogenesis imperfecta (OI), severe hypophosphatasia and the osteosclerotic disorders. **Table 3** summarizes the key findings on X-ray of various areas and their interpretation.

Following is a brief description of some of the common skeletal dysplasias presenting in children.

OSTEOPETROSIS

As the name implied, osteopetrosis is derived from Greek word *Osteo*—bone and *Petros*—stone, and therefore also known as *Marble Bone disease*. The radiographs are usually diagnostic and in some cases the condition was detected incidentally on skeletal radiograph performed for some other purpose. The new *Nosology* has two separate groups for skeletal dysplasia with increased bone density (Group 23 and 24). The Group 23 consists of osteopetrosis without modification of bone shape while Group 24 had metaphyseal and/or diaphyseal involvement. It thus became important to rule out metaphyseal or diaphyseal involvement to label a child or adult with osteopetrosis.

Condition can present at birth as neonatal form with complications like fractures, hypocalcemic, tetanic seizures and life-threatening bone marrow failure. The condition is caused by developmental failure of osteoclasts or its functions. The condition is inherited as an autosomal recessive (AR) (classical or malignant osteopetrosis), dominant or X-linked recessive. While AR osteopetrosis is rare but more severe, the dominant form is common (1 in 25,000) and can present in late childhood or adulthood. There are more than 15 genes identified which place the conditions into more distinct types. There are more than 21 subtypes of osteopetrosis. Moreover, the conditions need to be differentiated from other secondary causes of increased bone density as it occurs in fluorosis, lead and bismuth toxicity, Pagets disease and in malignancies. The diagnosis is based on clinical features and radiographs **(Fig. 1D)**.

Management of osteopetrosis is limited to supportive treatment and preventing complications. Hematopoietic stem cell transplantation (HSCT) is limited to certain severe form of osteopetrosis and even here it may not reverse the neuropathic involvement. Genetic counseling should be aimed at finding inheritance pattern and course and prognosis of with possibility of prenatal diagnosis (PND) in cases with known mutations.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is a group of heritable genetic disorders of collagen that mainly affect the bones and characterized by hypomineralization of the skeleton and was the first disorder hypothesized by McKusick to be due to a defect in collagen. The term *osteogenesis imperfecta* implies imperfect bone formation. Fractures are common, and in severe cases, can occur prenatally. Milder phenotype may have only a few fractures during life. The estimated

prevalence of the disorder is about 6–7 per 100,000 populations worldwide. OI Type II is also known as *Vroliks* disease and may have incidence of 1 in 60,000 births. One has to be careful in differentiating this condition from child abuse or battered baby syndrome.

Classification

Four types of OI were delineated by Sillence in late 1970s, but now we know of at least twelve recognized forms of OI, designated type I through type XI. Their classification and predominant phenotype is summarized in **Table 4**. While Type I is the mildest form of OI, type II is the most severe. Among all OI, types I and IV are the most common, affecting about 3–7 per 100,000 people. Genetic factors are increasingly being used to define the different forms of OI.

Etiopathogenesis

Osteogenesis imperfecta is caused due to mutations in the *COL1A1, COL1A2, CRTAP, and LEPRE1* genes. Moreover, *PPIB, FKBP10, SERPINH1*, and *SP7* mutations were also detected in few patients. More than 80–90% of cases of all OI have mutations in the *COL1A1* and *COL1A2* genes. These genes are involved in proteins that are used to assemble type I collagen which is the most abundant protein in bone, skin, and other connective tissues.

Majority of mutations that cause OI type I are due to abnormal *COL1A1* gene, while most cases of types II, III, and IV occur either due to the mutations in *COL1A1* or *COL1A2* gene. The characteristic features of OI are due to weakening of connective tissues, particularly in bone, due to type I collagen abnormality.

Table 1 Summary of groups of skeletal dysplasia classified as per nosology and classification of genetic skeletal disorders (2010)

Group No.	Group name	Representative dysplasia
1	FGFR 3 Chondrodysplasia	Achondroplasia
2	Type 2 Collagen defect	Achondrogenesis type 2
3	Type 11 Collagen defect	Stickler syndrome
4	Sulfation disorders	Diastrophic dysplasia
5	Perlecan	Schwartz Jampel
6	Aggrecan	SED/SEMD
7	Filamin	Melnick needles
8	TRPV4	Metatropic dysplasia
9	Short rib dysplasia	Ellis-van Creveld, SRP syndromes
10	Multiple epiphyseal dysplasia	MED/Stickler
11	Metaphyseal dysplasia	Schmid type/Cartilage hair hypoplasia
12	Spondylometaphyseal dysplasia	SMD many types
13	Spondylo-epi-(meta)-physeal dysplasia	Dyggve-Melchior-Clausen
14	Severe spondylodysplastic dysplasia	Achondrogenesis, SMD
15	Acromelic dysplasia	Acrodysostosis
16	Acromesomelic dysplasia	Grebe dysplasia
17	Mesomelic and rhizomesomelic dysplasia	Langer type Robinow syndrome
18	Bent bone dysplasia	Campomelic dysplasia
19	Slender bone dysplasia	3-M syndrome
20	Dysplasia with multiple joint dislocations	Desbuquois syndrome (type 1)
21	Chondrodysplasia punctata	CDP many types
22	Neonatal osteosclerotic dysplasia	Caffey disease Raine dysplasia
23	Increased bone density group (no modification of bone shape)	Osteopetrosis
24	Increased bone density with meta/diaphyseal involvement	Juvenile Paget disease
25	Osteogenesis imperfecta	OI, Ehlers-Danlos syndrome
26	Abnormal mineralization	Hypophosphatasia
27	Lysosomal storage disorders	MPS/fucosidosis
28	Osteolysis group	Mandibuloacral osteolysis
29	Disorganized development of skeletal components	Multiple cartilaginous exostoses, FOP
30	Overgrowth syndrome with skeletal involvement	Weaver, Sotos, Proteus syndromes
31	Genetic inflammatory/Rheumatoid like osteoarthropathies	Progressive pseudorheumatoid dysplasia
32	Cleidocranial dysplasia	Cleidocranial dysplasia
33	Craniosynostosis syndrome	Pfeiffer, Apert, Crouzon syndromes
34	Dysostoses with predominant craniofacial involvement	Treacher Collins syndromes
35	Dysostoses with predominant vertebral involvement	Spondylocostal dysostosis
36	Patellar dysostoses	Nail patella syndrome
37	Brachydactylies	Brachydactyly many types
38	Limb hypoplasia-reduction defects	Ulnar mammary syndrome
39	Polydactyly, syndactyly, triphalangism	Meckel syndrome
40	Defects in joint formation	Multiple syostosis syndrome

Abbreviations: OI, osteogenesis imperfect; USG, ultrasonography; SRP, short rib polydactyly; SED, spondyloepiphyseal dysplasia; FOP, fibrodysplasia ossificans progressive; SMD, spondylometaphyseal dysplasias; FGFR, fibroblast growth factor receptor.

Table 2 Skeletal dysplasia: Clinical workup, key findings, and suggestive conditions

Parameter	Key findings	Suggestive conditions
Family history to ascertain genetic mechanisms including chromosomal duplication/deletion, germline mosaicism, uniparental disomy	Other affected family member, consanguinity, look for mild features of the disorders in other members	Pattern of inheritance in AR and dominant conditions can be ascertained
Onset of short stature	Prenatal, postnatal and age of onset	Milder disorders may not be detected till late in life. Antenatal onset may be more severe
Part of body involved	Rhizomelic (humerus and femur)	Achondroplasia, thanatophoric, OI, chondrodysplasia punctata, Jeune disease, atelosteogenesis
	Mesomelic (radius, ulna, tibia, fibula)	Langer dysplasia due to SHOX mutation, dyschondrosteosis (Leri-Weil disease): limb shortening with a Madelung deformity
	Acromelic (hands and feet)	Weill-Marchesani syndrome (WMS), geleophysic dysplasia (GD) and acromicric dysplasia (AD)
Nonlimb shortening		Certain OI
Head and facial dysmorphism	Frontal bossing and flattened nasal bridge	Achondroplasia
	Cleft palate and micrognathia	Type II and XI collagen defects
	Severe abnormally flattened midface with upturned nose	Chondrodysplasia punctata
	Swollen ear pinnae in neonatal period	Diastrophic dysplasia
Congenital heart defects	Complex outlet defects, VSD	Chondroectodermal dysplasia and short rib polydactyly disorders, Larsen syndrome
GI abnormalities	Congenital megacolon	Cartilage hair hypoplasia
	Malabsorption syndrome	Shwachman-Diamond syndrome
	Omphalocele	Otopalatodigital, atelosteogenesis I/Bloomberg

Mutations in the *CRTAP* (type VII) and *LEPRE1* genes (type VIII) are responsible for rare, often severe cases of autosomal recessive osteogenesis imperfecta. OI without known mutations in the *COL1A1, COL1A2, CRTAP, or LEPRE1* gene, are classified types V and VI. Molecular biologists are trying to identify additional genes that may be responsible for these conditions. Taking clue that type I collagen fibers are also found in skin besides the bone, attempts have been made to use skin amenable as *topical optical biopsy* using nonlinear microscopy to diagnose severity of OI. It was shown that nonlinear microscopy techniques if used in association with specific scoring methods may prove to be a noninvasive tool to distinguish the different types of OI in human skin and found to have good correlation with patient's clinical severity. Furthermore, these innovative methods may also help in understanding the etiopathogenesis in greater detail for clinical management.

Clinical Features

Osteogenesis imperfecta type I and milder forms are characterized by bone fractures during childhood and adolescence and become less frequent in adulthood. Affected persons may have a blue sclera, may develop progressive hearing loss in adulthood and may have near normal height.

Severe forms may have frequent bone fractures that may begin even before birth and result from little or no trauma. They may also have blue sclerae, short stature, hearing loss, respiratory problems, and a may have dental problems. The most severe forms, type II, can include an abnormally small, fragile rib cage and underdeveloped lungs leading to life-threatening problems with respiration in infancy associated with high mortality. Other problems are *ligamentous laxity* (loose ligaments), muscle weakness, thinness of the sclera, and hence care during eye surgery.

The clinicoradiological features of OI type III are shown in **Figure 2**.

Diagnosis

Patients most commonly present with fractures after minor trauma. Some of unique features of OI are as follows:
- There is a tendency for easy bruising because of deficiency in collagen in dermal tissues
- Though fractures are common after mild trauma but these fractures also heal readily
- Deafness may occur in 50% of patients with type I OI by age 40 years
- X-rays are diagnostic (already detailed under skeletal survey)
- Antenatal ultrasonography (USG) may detect fractures in severe form of OI (type II).

Measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DEXA) provide some guidance about degree of osteoporosis and fracture rate but normative data for young children are not available.

It is also important for the pediatrician to differentiate fractures of bone disease (OI and some metaphyseal dysplasia) from child abuse and neglect (CAN) or battered baby syndrome. At times it may be difficult to differentiate the two conditions solely based on pattern and sites of fractures. A systematic review recently suggested keeping child welfare a top priority as CAN may be common and associated with higher mortality whereas bone disease is a diagnosis of exclusion.

Management

The mainstay of treatment is a multidisciplinary approach reducing the number of fractures, surgical correction addressing deformity, maximizing function, and improving quality of life.

Medical Therapy

Bisphosphonates are now commonly prescribed to individuals with OI. A recent Cochrane review concluded that oral or intravenous bisphosphonates increase BMD in children and adults with this condition. These were not shown to be different in their ability to increase BMD. It is unclear whether oral or intravenous bisphosphonate treatment consistently decreases fractures, though
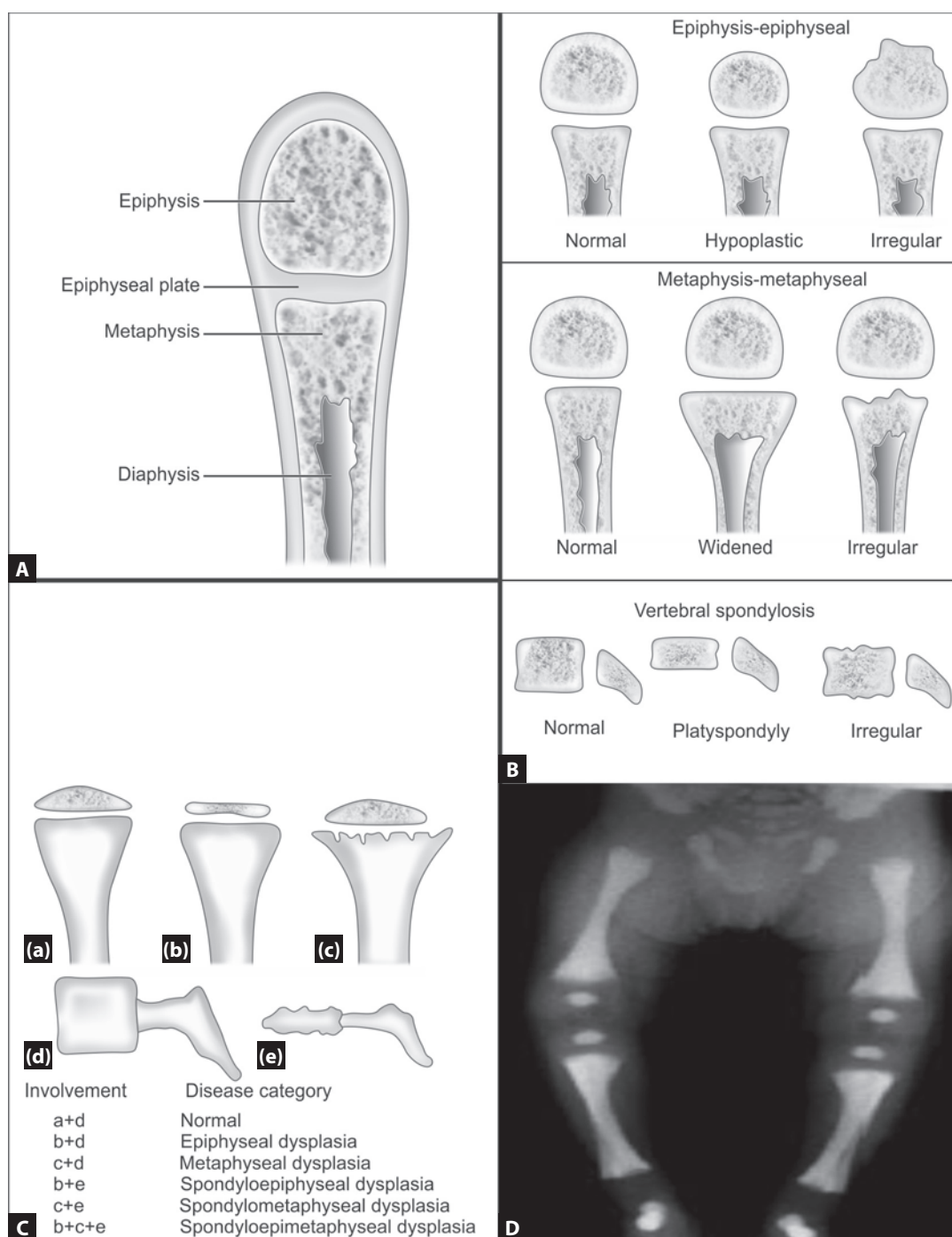
Figures 1A to D Radiologic assessment of skeletal dysplasia. (A) Key areas of the growing bone; (B) Radiographic manifestations of dysplasias; (C) Radiographic abnormalities helpful in classification of skeletal dysplasias; and (D) Osteopetrosis, generalized osteosclerosis
(Reproduced with permission from: Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. J Clin Res Pediatr Endocrinol. 2011;3:163-78.)

multiple studies report this independently and no studies report an increased fracture rate with treatment. The studies included here do not show bisphosphonates conclusively improve clinical status (reduce pain; improve growth and functional mobility) in people with osteogenesis imperfecta. However, given their current widespread and expected continued use, further research is needed for the long-term safety, efficacy, fracture reduction and improvement in quality of life indicators. While considering bisphosphonates, precautions to be taken to discontinue them

prior to surgery since they interfere with normal healing. They can be resumed once healing completed.

It is important to identify and protect bones at risk from fractures and progressive deformities. The surgical intervention mainly involves *intramedullary fixation* methods to fix fractures or perform deformity correction. The *Fassier-Duval telescopic intramedullary system* is one of the more popular methods used by surgeons who deal with appendicular deformity corrections in OI.

Table 3 Workup of patient with suspected skeletal dysplasia

Area to be X-rayed	Key findings	Interpretation
Skull	Cranial sutures for craniosynostoses and presence of intersutural or Wormian bones in the lambdoid sutures	Flattening of the anterior margin of the sella on the lateral view (J-shaped sella) can represent a normal variant or can be seen with certain dysplasias such as the MPS
	Overall skull mineralization, thickness of the calvarium, and craniofacial proportions for frontal bossing, midface hypoplasia, mandibular hypoplasia, and retrognathia	
	Shape of the sella turcica	
Ribs, rib cage	Assessment of the number, shape (shortened, thickened, or gracile appearance), and morphology (fusions) of the ribs and clavicle	Scapular hypoplasia and clavicular absence or hypoplasia—cleidocranial dysplasia; severe hypoplasia of the scapula is seen in camptomelic dysplasia and Antley-Bixler syndrome
	Cardiac silhouette and lungs	Holt-Oram syndrome and Ellis-van Creveld syndrome
	Short ribs	Short-rib polydactyly syndromes, asphyxiating thoracic dysplasia, chondroectodermal dysplasia, metaphyseal dysplasia (associated with immune defect), and metatrophic dysplasia
Cervical spine	Ossification and shape of the dens for odontoid dysplasia and cervical instability, which may be observed in several dysplasias	e.g., mucopolysaccharidoses, spondyloepiphyseal dysplasia congenita, pseudoachondroplasia, metatropic dysplasia, and diastrophic dysplasia
Spine (AP and lateral)	Curvature, gibbus Platyspondyly (flattening of the vertebral body): (1) Without associated epiphyseal or metaphyseal abnormalities; (2) With associated epiphyseal or metaphyseal abnormalities	Severe platyspondylia may be observed in metatrophic dysplasia, lethal perinatal osteogenesis imperfecta, thanatophoric dysplasia, short rib polydactyly syndromes, SED congenita, other types of SED, and Kniest dysplasia
	Coronal clefting (vertical lucency within the vertebral body on the lateral view)	Kniest, metatropic, and desbuquois dysplasia
	Narrowing of the interpediculate distance caudally on the AP view (suggests spinal stenosis)	Suggests achondroplasia and diastrophic dysplasia
	Note for posterior scalloping of vertebral bodies, endplate irregularity, anterior beaking of vertebral bodies, anterior and posterior wedging of vertebral bodies, and tall vertebral bodies	Seen in several skeletal dysplasia
	Fusion and segmentation anomalies	Klippel-Feil or VACTERL and other disorders of organogenesis
	Absence of calcification of vertebral bodies	Achondrogenesis types I and II
Pelvis	Absence or delay of ossification of the pubic bone in association with poor ossification of other parts of the skeleton in the neonate	Cleidocranial dysplasia
	Misshapen iliac bones and short and wide iliac bones with narrow sacrosciatic notches	Thanatophoric dysplasia, achondroplasia
	Abnormal pelvic configuration (small sacrosciatic notches)	Achondroplasia, Ellis-van Creveld syndrome, metatrophic dysplasia, thanatophoric dysplasia, and Jeune syndrome
	A flat or steep appearance or presence of marginal irregularity	Jeune syndrome
Extremities	Should be evaluated for rhizomelia (relative shortening of the proximal extremities: humerus, femur), mesomelia (relative shortening of the middle portions of the extremities: radius, ulna, tibia, fibula), acromelia (relative shortening of the distal extremities), acromesomelia, and micromelia (generalized shortening of all extremities)	
	Oval translucent area in proximal femora and humeri	Achondroplasia
	Dumbbell-shaped appearance of long bones	Kniest dysplasia and metatrophic dysplasia
	Bowing of limbs (camptomelia)	Camptomelic dysplasia, osteogenesis imperfecta syndromes, and thanatophoric dysplasia
	Calcified projections (spikes) at lateral femoral metaphyses	Thanatophoric dysplasia and achondrogenesis types I and II
	Cupping of the ends of the rib and long bones and metaphyseal flaring	Achondroplasia, metaphyseal dysplasias, asphyxiating thoracic dysplasia, and chondroectodermal dysplasia
	Long bone fractures	Osteogenesis imperfecta syndromes, hypophosphatasia, osteopetrosis, and achondrogenesis type I (Parenti-Fraccaro syndrome)
	Absence of epiphyseal ossification centers	SED congenita, multiple epiphyseal dysplasia, and other SED (unspecified)
	Cone-shaped epiphyses	Acrodysostosis, cleidocranial dysplasia, and trichorhinophalangeal dysplasia

Contd...

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Area to be X-rayed	Key findings	Interpretation
	Proximal pointing of the metacarpals	Dysostosis multiplex
	Stippling of the epiphyses	Chondrodysplasia punctata and other nonskeletal dysplasia syndromes, such as cerebrohepatorenal syndromes, warfarin-related embryopathy, chromosomal trisomy (trisomy 21, trisomy 18), lysosomal storage diseases (generalized gangliosidosis), phenytoin-induced embryopathy, Smith-Lemli-Opitz syndrome, anencephaly, cretinism, multiple epiphyseal dysplasia, SED, and normal variant hypoparathyroidism
	Polydactyly	Short rib polydactyly syndrome
	Diplicated calcaneus	Larsen syndrome

Abbreviation: SED, spondyloepiphyseal dysplasia.

Table 4 Classification of osteogenesis imperfecta

Osteogenesis imperfecta type	Inheritance	Phenotype	Gene defect
Classical Sillence types			
I	AD	Mild	Null *COL1A1* allele
II	AD	Lethal	*COL1A1* or *COLI1A2*
III	AD	Progressive deforming	*COL1A1* or *COLI1A2*
IV	AD	Moderate	*COL1A1* or *COLI1A2*
Unknown etiology			
V	AD	Distinctive histology	Unknown
Mineralization defect			
VI	AR	Mineralization defect, distinctive histology	*SERPINF1*
3-hydroxylation defects			
VII	AR	Severe (hypomorphic) Lethal (null)	*CRTAP*
VIII	AR	Severe to Lethal	*LEPRE1*
IX	AR	Moderate to lethal	*PPIB*
Chaperone defects			
X	AR	Severe to lethal	*SERPINH1*
XI	AR	Progressive deforming (Bruck syndrome 1)	*FKBP10*
Unclassified OI or Collagen based disorders			
Bruck syndrome 2	AR	Joint contractures	*PLOD2*
Caffey disease	AD	Cortical hyperostosis	*COL1A1*
Osteoblast maturation defects	AR	Moderate	*SP7*

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

ACHONDROPLASIA

Achondroplasia is the most common skeletal dwarfism (Online Mendelian Inheritance in Man [OMIM] 100800) and most common to survive. They can be part of a circus or movie as an adult with childish proportions. It is also the most common form of disproportionate short stature. Its incidence can be 1 in 15,000 to 1 in 40,000 live births. Achondroplasia is caused by a gene abnormality in the fibroblast growth factor receptor 3 (*FGFR3*) gene which makes the protein with same name converting cartilage to bone. This gene was discovered during search for Huntington disease gene and located on Chromosome 4. *FGFR3* is the only gene known to be associated with achondroplasia.

Etiopathogenesis

Achondroplasia is inherited as autosomal conditions showing complete penetrance with most cases due to new mutation. Paternal age effect on mutation was noted by *Penrose* (1955). Gonadal mosaicism is a known risk factor for recurrence of achondroplasia in the sibs from unaffected parents. In achondroplasia, the new mutations are of paternal origin possibly due to *mutator* gene acting in male meiosis. Other people with achondroplasia inherit the condition from a parent who has achondroplasia.

Clinical Features

Though inappropriate diagnosis of achondroplasia is made in children with short stature, the condition is quite distinctive being characterized by rhizomelic short limbs, a large head with frontal bossing, hypoplasia of the midface and a trident configuration of the hands **(Fig. 3)**. While there is hyperextensibility of most joints, but extension and rotation are limited at the elbow. Mild to moderate hypotonia is common, and motor milestones are usually delayed but intelligence is normal unless complicated by associated CNS abnormalities like hydrocephalus.

Characteristic radiological features include caudad narrowing of the inter-pediculate distance, rather than the normal caudad widening and a notch like sacroiliac groove. Also in children, epiphyseal ossification centers show a circumflex or chevron seat on the metaphysis.

Megalencephaly occurs in achondroplasia indicating that genes not only affect skeletal system but also have systemic effects. In some cases, internal hydrocephalus results due to disparity in size of skull base and brain. The hydrocephalus results from increased intracranial venous pressure due to stenosis of the sigmoid sinus at the level of the narrowed jugular foramina. It is recommended that in the management of achondroplastic infants, USG be done at birth and at 2 months and 4 months. The brainstem compression is more common in achondroplasia than thought and may be responsible for the abnormal respiratory function and sleep problems. It is notable that evidence of respiratory dysfunction detected by polysomnography (PSG) has

Figures 2A to E (A) Osteogenesis imperfecta (OI) type III. Fixation of fractured femur; (B) OI type III age 6 years: Bowed legs; (C) Bowed legs and fracture, OI type III; (D) OI type III: Blue sclera; and (E) OI type III in an adult with severe short stature and deformities

Figure 3 Achondroplasia—See large head, shortening of limbs with multiple skin folds (*Courtesy: Dr Varun Alwadhi*)

also been found to be responsible for the reduced mental capacity in these patients.

Diagnosis

The diagnosis of achondroplasia based on the typical clinical and radiologic features may not be difficult. The mutations causing achondroplasia can be easily detected by molecular diagnosis (1 polymerase chain reaction [PCR] and 1 restriction digest).

Management

Recommendations for follow-up and management were reviewed at the first international symposium on achondroplasia in 1988 and 1993. Health Supervision Guidelines were issued by American Academy of Pediatrics in 1995 and modified in 2005. The recommendations included: measurements of growth and head circumference using growth curves standardized for achondroplasia; careful neurologic examinations (including computed tomography [CT], magnetic resonance imaging [MRI], somatosensory evoked potentials and PSG) and surgical enlargement of the foramen magnum in cases of severe stenosis;

management of frequent middle ear infections and dental crowding; measures to control obesity starting in early childhood and speech therapy. Controlled trials of growth hormone treatment of children with achondroplasia have shown to improve height during 4 years of therapy without adverse effect on trunk-leg disproportion. Limb-lengthening and deformity correction can be safely performed in appropriate cases with surgical intervention.

As the molecular pathogenesis of achondroplasia is being elucidated, there is shift of interest to medical therapy aimed at chemical inhibitors for the FGFR3 tyrosine kinase, blocking antibodies to interfere with binding of FGF ligands to FGFR3 and use of C-type natriuretic peptide (CNP; 600296). Attempts are also being made to use World Health Organization (WHO) International Classification of Functioning, disability, and health (ICF) model for optimal management of such individuals.

Prognosis

The risk of sudden unexpected death in infants with achondroplasia is high in first year attributable to abnormalities at the craniocervical junction causing cervical cord compression. The best predictor for need for neurosurgical suboccipital decompression included lower-limb hyper-reflexia or clonus on examination, central hypopnea demonstrated by PSG studies, and foramen magnum measurements below the mean for children with achondroplasia.

The overall mortality between ages 20 years and 35 years is 10 times higher than in the general population. Achondroplasia is also associated with increased incidence of obesity. Average life expectancy is decreased by 10 years.

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Genetics

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic condition of abnormal ossifications of body tissues. It has an autosomal dominant inheritance with complete penetrance and having variable expression. Gonadal mosaicism has also been suggested. Most cases are de novo mutations. However, it can be caused by mutation in the bone morphogenetic protein type 1 receptor *ACVR1* (OMIM 102576) gene located on chromosome 2q24.1.

Clinical Features

It is a rare, congenital disorder with onset in infancy or childhood. The disease manifests with progressive heterotopic ossification and Hallux valgus. The heterotopic ossifications are common and if appears in the spine or thoracic area, trunk deformity and severe respiratory problems may occur. In general, heterotopic ossification first occurs during infancy and later childhood, following subcutaneous swelling and sclerosis (flare-ups) often triggered by trauma, invasive wounds such as bruising, and surgery. Ossification may also result in trismus.

Classic FOP have congenital malformations of the great toe (short and malformed, often with only one phalanx) **(Fig. 4A)**; and progressive heterotopic ossification **(Fig. 4B)**. Painful inflammatory swelling and subsequent calcification **(Fig. 4C)** and ossification of fasciae, tendons and muscles, in tissues of neck, trunk, limbs, lead to progressive immobilization. The *FOP-plus* (classic defining features of FOP plus one or more atypical features) and *FOP variants* (major variations in one or both of the two classic defining features of FOP) have been described. All these cases had heterozygous ACVR1 missense mutations in conserved amino acids. Severe cases with widespread, rapidly progressive ectopic calcifications detected shortly after birth have been described. Calcifications did not involve internal organs and skin.

Diagnosis

The disease needs to be distinguished from the familial ectopic ossification which is benign and without additional symptoms; and from myositis ossificans which occurs following trauma. X-ray in FOP shows soft tissue calcification **(Fig. 4)**, short broad femoral necks, and small and abnormal cervical vertebral bodies. Frequently there may be microdactyly or adactyly of thumbs and great toes.

DYSOSTOSIS MULTIPLEX

Dysostosis multiplex is radiological manifestation of a group of disorders that results in the intralysosomal accumulation of a variety of complex carbohydrates, all of which have similar skeletal manifestations. The recent revision of *Nosology 2011* has classified dysostosis multiplex under *Group 27 as lysosomal storage diseases* with skeletal involvement. They have characteristic skeletal features **(Table 5)**. The skull is enlarged with thick diploe and J-shaped sella turcica. In the chest, the ribs are oar-shaped, the clavicles are wide and the scapulae are thick. Vertebral bodies are often ovoid with anterior hook-like projections **(Fig. 5A)**. The inferior ilia are constricted and the iliac wings are flared **(Fig. 5B)**. The long tubular bones show irregular diaphyseal modeling, submetaphyseal constriction and shortening. The short tubular bones demonstrate metaphyseal widening and epiphyseal dysplasia; the proximal 2nd through 5th metacarpal bones are tapered **(Fig. 5C)**. Overall bones are demineralized with coarse trabeculation.

CLEIDOCRANIAL DYSPLASIA

Cleidocranial dysplasia or dysostosis is a condition that mainly affects clavicle, teeth and cranium. Disease can have varied presentation. They have been classified under *Group 32* of the current nosology.

Individuals with cleidocranial dysplasia have poorly developed or absent clavicles **(Fig. 6A)**. They have narrow shoulders and delayed closing of fontanels **(Fig. 6B)**. They also have brachycephaly, frontal bossing, a flat nose, and a small maxilla. They have short stature with short, tapered fingers and broad thumbs; short forearms; flat feet; knock knees; and scoliosis of spine. Individuals may also have osteoporosis **(Fig. 6C)**. Due to narrow pelvis, women with cleidocranial dysplasia have difficulty in vaginal delivery and therefore increasingly require a cesarean section when delivering a baby.

Dental abnormalities are common in this condition with unusually shaped, peg-like teeth, misalignment of the teeth and malocclusion **(Fig. 6D)**; and extra teeth, sometimes accompanied by cysts in the gums. They also can have hearing loss and recurrent ear infections.

The condition is usually inherited as an autosomal dominant condition. The *RUNX2* gene is involved which provides instructions for making a protein that is involved in bone and cartilage development and maintenance. In about 30% of individuals no mutation in the gene has been found and cause remains unknown. Certain conditions in this group also shows autosomal recessive pattern, e.g., Craniosynostosis, delayed fontanel closure, anal-genital abnormalities and skin eruptions (CDAGS) syndrome.

CRANIOSYNOSTOSIS SYNDROMES

Craniosynostosis consists of premature fusion of one or more cranial sutures, often resulting in an abnormal head shape **(Fig. 7)**. According to recent classification, they have been kept under *Group 33* of 2011 Nosology. They may be either a primary craniosynostosis (due to primary defect) or, secondary craniosynostosis (due to small brain). When only one suture fuses prematurely, it is termed as simple craniosynostosis. Complex or
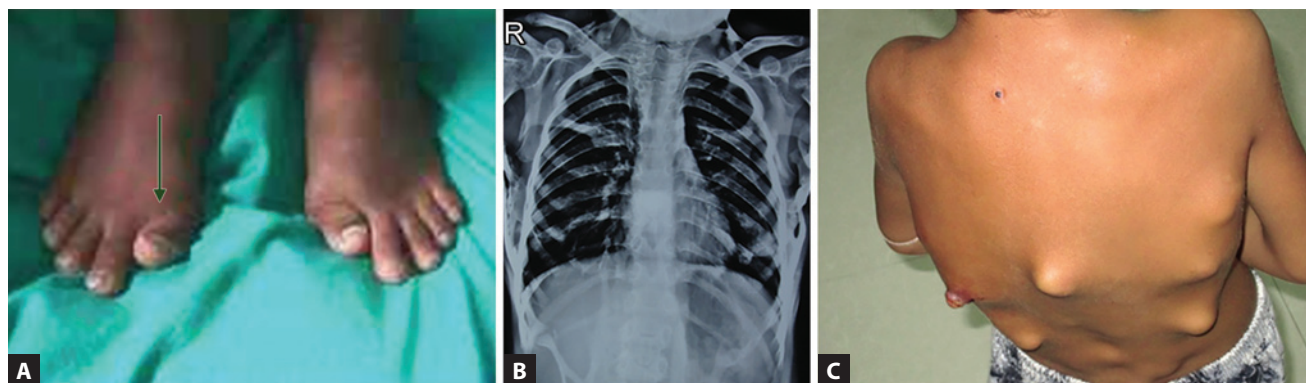
Figures 4A to C Fibrodysplasia ossificans progressiva. (A) Showing bilateral (B/L) hallux valgus; (B) Radiograph of chest showing heterotopic ossifications; and (C) Calcifications of tissue

Figures 5A to C Radiological features of dysostosis multiplex. (A) Ovoid vertebra showing anterior hook like presentations; (B) Pelvis with flaring of ileal wings; and (C) V-shaped deformity due to hypoplasia of ulna and proximal tapering of metacarpals

Table 5 Dysostosis multiplex

Skull	Macrocephaly with dolicocephaly
	Vertical frontal crest
	Abnormal J-shaped sella turcica
	Thickened cortical bone
	Facial anomalies
	• Lack of pneumatization of mastoid process cells and of paranasal cavities
	• Obtuse mandibular angle with prognathism
	• Teeth widely spaced
Thorax	Paddle-shaped or oar-shaped ribs (widened anteriorly and tapered posteriorly)
	Short and thickened clavicles
Spine	*Craniovertebral junction*: Atlantoaxial instability, stenosis and compression of the spinal cord
	Thoracolumbar spine: Gibbus
	Malformations of the vertebral bodies
Pelvis	Rounded iliac wings
	Inferior tapering of the ileum
	Hip dysplasia
	• Poorly developed acetabulum
	• Underdevelopment of the medial portion of the proximal femoral epiphysis
	• Coxa valga
Long bones	Mildly hypoplastic epiphyses
	Proximal humeral notching
	Long and narrow femoral neck
Knees	Genu valgum
Hands and feet	V-shaped deformity of the hypoplastic distal ulna and radius
	Hypoplastic and irregularly-shaped carpal and tarsal bones
	Proximal pointed metacarpals and metatarsals
	Bullet-shaped phalanges

compound craniosynostosis, on the other hand, is used to describe when premature fusion of multiple sutures occurs. When children with complex craniosynostosis also display other body deformities, it is labeled as *syndromic* craniosynostosis. Apert, Pfeiffer, Crouzon, Antley-Bixler, Shprintzen-Goldberg are some of the syndromes. They may be due to mutations of *FGFR3* gene mutations or *POR, TWIST1 or MSX2* gene.

The management consists of careful monitoring and observing for development of elevated intracranial pressure. Surgical management consists of craniofacial corrections if indicated preferably within first year.

ECTRODACTYLY

This has been classified under *Group 38—limb hypoplasia-reduction defects* under recent Nosology. The other conditions under the Group are Holt-Oram syndrome, Fanconi anemia, thrombocytopenia absent radius (TAR) syndrome, amelia, tetramelia, and acheiropodia, etc.

Ectrodactyly, also known as lobster deformity, may affect hand, foot or both **(Fig. 8)**. The condition should prompt us to look for other associated abnormalities of heart, brain, genitourinary and skin involvement. Common human genetic disorders with ectrodactyly include isolated spilt hand/foot malformations (SHFM), ectrodactyly-ectodermal dysplasia, and various other SHFM syndromes.

HANDIGODU SYNDROME

Handigodu syndrome (HS) is a crippling disorder reported from the *Adi Karnataka community* of Karnataka, India. It is named after the village of Handigodu, in Shimoga district of the state of Karnataka where it was first noticed. HS also has some similarity to Mseleni joint disease in the Zululand of South Africa.
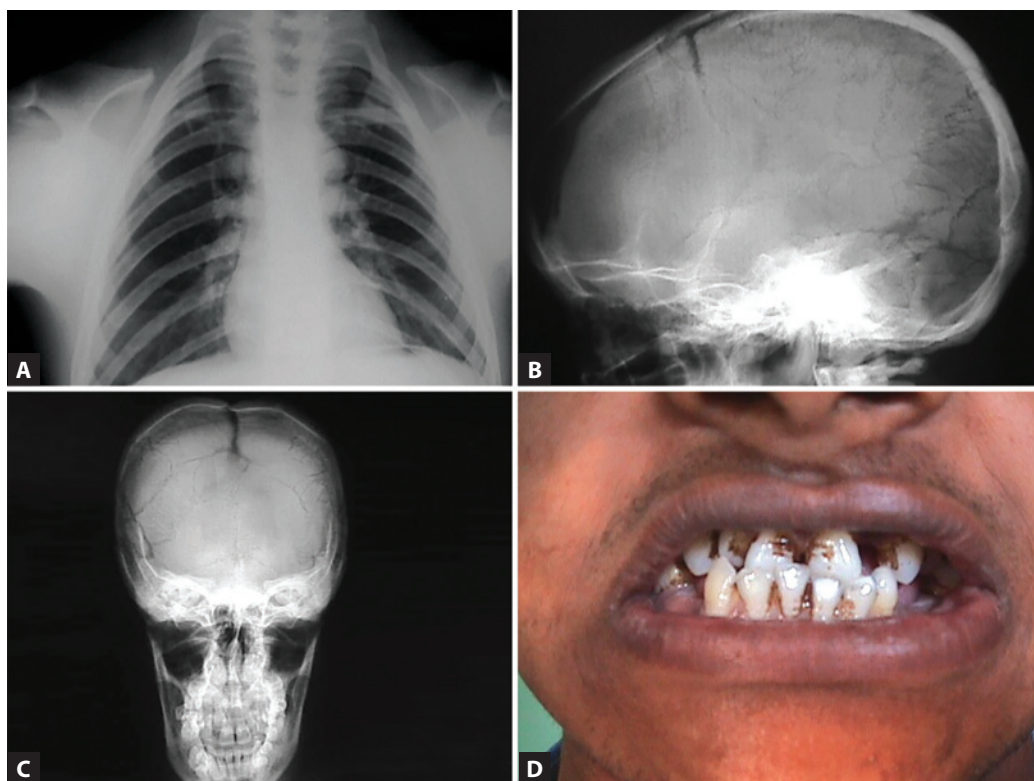
Figures 6A to D Cleidocranial dysostosis. (A) Absent clavicles; (B) Open anterior fontanel in adulthood; (C) Wormian bones; and (D) Dental malocclusion

Figure 7 An 8-month-old boy with craniosynostosis resulting in clover shaped deformity of skull

Figure 8 Ectrodactyly of foot

Handigodu syndrome cases have been reported from Sagar taluk of the Shimoga District, and Sringeri, Koppa, and NR Pura taluks of Chikmagalur District (Karnataka). The disease particularly affects laborers living on the Western Ghats and Chanangi and Chaluvadi are the two lower socioeconomic communities most affected. The disability is progressive and more than 1,000 people have been killed since it was first noticed in January 1975. Four laborers were brought with severe intolerable pain and difficulty in movements. Within a week there were 30 more cases. Considering the condition to be a neurological disease, experts from National Institute of Mental Health and Neurosciences (NIMHANS) were called who ruled out it to be a nervous system disorder. Scientists from National Institute of Nutrition were assigned by the Director General, Indian Council of Medical Research (ICMR) for further investigations. Preliminary study showed relationship with eating crabs by these people and possibility of pesticide toxicity. However, they finally concluded it to be genetic condition as it was familial and occurring in same tribal population. Dr SS Agarwal and his team from Lucknow (Uttar Pradesh, India) studied the clinical picture along with X-rays and delineated the condition in detail. The research is still going on for this mystery disease.

Clinical Features

Handigodu syndrome is now considered as an inherited degenerative osteoarthropathy (OMIM 6133430). The malady present as a progressive skeletal system disorder with severe pain and locomotion limited to moving in squatting posture. A locomotor disability also affects their routine and they have growth failure. On the basis of anthropometric and X-ray analysis, HS is subdivided into three groups by Agarwal et al:

1. Type 1: Arthritic form
2. Type 2: Dysplastic form
3. Type 3: Dwarf type.

Handigodu syndrome is having an autosomal dominant inheritance as determined by pedigree analysis but its molecular basis is not yet mapped. The suggestion that environmental factors (eating crabs and pesticides) may play role in HS also seems to be unclear. Current research is focused on studying biochemical markers which may predict the development of disease in susceptible population. Hypocalcitoninemia is one such marker studied in these affected individuals. HS patients are currently treated symptomatically for their pain.

SHORT RIB DYSPLASIAS

Short rib polydactyly (SRP) syndrome, also includes asphyxiating thoracic dysplasias (Jeune type), presenting at birth and have fatal outcome during newborn period. The current *Nosology* classify them under Group 9 as short-ribs dysplasias (with or without polydactyly). This group also includes chondroectodermal dysplasia (Ellis-van Creveld syndrome). There are now more than 10 conditions included in the group. Detail phenotypic workup of these conditions has earned them the name of scientists who initially delineated the condition. Notable contribution is of Dr IC Verma who in 1975 studied a consanguineous family in which 6 of 9 pregnancies had lethal form of severe shortening of limbs and thorax. He distinguished this condition from a similarly reported SRP syndrome by Saldino and Noonan in 1972. Thus, this dysplasia was classified as short rib polydactyly syndrome (SRPS) type 3 (Verma-Naumoff). This also encouraged the budding medical geneticist to go for detail study of these conditions. It was also felt that detail fetal autopsy will also uncover many changes in other organs in newborn presenting with short ribs which will be helpful for correct diagnosis and thereby appropriate counseling.

Most of the short ribs dysplasia present with extremely short limbs, with or without polydactyly and with funnel shaped with hypoplastic lungs causing respiratory problems. Besides the constant features, associated abnormalities in several organs may be present with varying degree of involvement.

ANTENATAL DIAGNOSIS OF SKELETAL DYSPLASIA

Antenatal diagnosis of skeletal dysplasias may pose a complex problem. Although USG has proved to be a noninvasive method for the antenatal diagnosis, the accurate diagnosis of a dysplasia may be difficult to make before birth especially in couple without a familial history. This is due to the fact that they have varied phenotypic presentations, have variability in the time of manifestation and often, there is lack of specific molecular markers. However, it is important to establish lethality of condition since most of these dysplasias have fatal outcome or severe disability. USG may also aid in assessing the lethality of the dysplasia. Features suggesting lethality on USG are summarized in **Table 6**.

Often pediatricians are consulted as a part of team dealing with suspected skeletal dysplasia. Parents may be concerned about the survival as well as disability in terms of short stature or other

Table 6 Ultrasonographic parameter for lethality

Parameter	Findings
Chest biometry/features	Thoracic circumference below *the fifth percentile* (measured at the level of the four-chamber heart view)
	Thoracic-to-abdominal circumference ratio less than 0.6–0.79
	Short thoracic length
	Chest: trunk-length ratio equal to or less than 0.32
	Ribs encircling less than 70% of chest conference (at level of four-chamber heart view)
	Markedly narrowed anteroposterior thoracic diameter in the sagittal view
	Concave or bell-shaped contour of the thorax in the coronal view
	The ratio of (chest area − heart area)/chest area being below the fifth percentile
Lung biometry (suggestive of lung hypoplasia)	Lung area below the fifth percentile
	Right lung area: Thoracic area ratio below 0.11
	Right lung diameter below the fifth percentile
Limb/body ratios	Femur length/abdominal circumference <0.16
Doppler evaluation	Distal pulmonary arteries
	Tracheal fluid flow
Compressibility of calvarium with USG probe	Low mineralization in OI type II, achondrogenesis and hypophosphatsia

NB: Earlier the age at detection, more likely to be a lethal skeletal dysplasia

abnormalities. As part of workup of these suspected dysplasia, USG has been recommended as an investigation of choice coupled with fetal echocardiography (ECHO), genetic consultation and counseling for genetic testing wherever possible and low dose CT (total X-ray dose not to exceed 2.5–4.5 mSu) under professional judgment. Repeat USG at 32 weeks and X-ray if diagnosis not confirmed for purpose of prognosis may be considered.

An algorithm for diagnosis of skeletal dysplasia based on antenatal USG is depicted in **Flow chart 1**.

A large number of fetus with skeletal dysplasia die in utero. Establishment of accurate diagnosis will require a diagnostic autopsy workup. If parents do not consent for a detail pathologic examination, a minimal postmortem (autopsy) workup should be suggested that include (1) baby/fetus photographs; (2) baby gram; and (3) blood/tissue specimens for chromosome/genetic analysis or preservation of fibroblasts later studies.

CONTEMPORARY APPROACHES FOR IDENTIFYING SKELETAL DYSPLASIA

Our current understanding of many fundamental mechanisms underlying mammalian physiology has been profoundly influenced by discoveries in human genetics. Recent improvements in the speed and accuracy of DNA sequencing, together with increasingly sophisticated mathematical approaches for annotating gene networks, have revolutionized the field of human genetics and made these once time consuming approaches accessible to most investigators. It is possible to get one's own genome commercially for approximately ₹ 250,000 around this point in time. In the field of bone research, a particularly active area of gene discovery has occurred in patients

Flow chart 1 Algorithm for approaching fetal dysplasia based on limb bone density, part affected and bowing
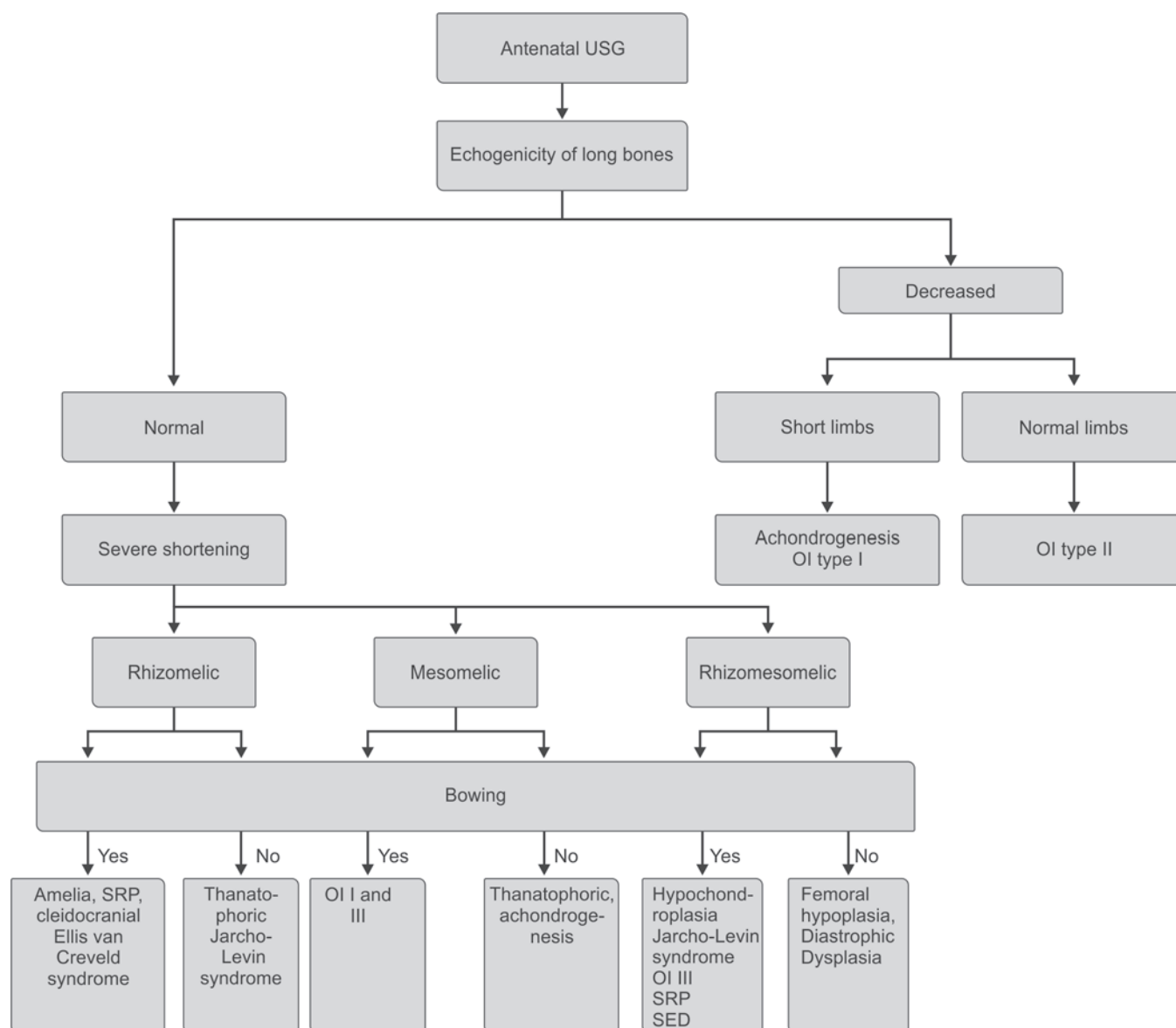
Abbreviations: OI, osteogenesis imperfect; USG, ultrasonography; SRP, short rib polydactyly; SED, spondyloepiphyseal dysplasia.

Table 7 Summary of management of skeletal dysplasia

Condition	Medical	Surgical	Remarks
Prenatal detection	Resuscitation, supportive	Achondroplasia—LSCS	Counseling and continuing support
Osteogenesis imperfecta	Cyclic administration of intravenous pamidronate reduces the incidence of fracture and increases bone mineral density, while reducing pain and increasing energy levels Doses vary from 4.5–9 mg/kg/year	Surgical interventions include intramedullary rod placement, surgery to manage basilar impression, and correction of scoliosis Use of the new extensible Fassier-Duval rods for intramedullary fixation has shown promising results in these patients with early ambulation and reduced deformity especially in patients with appropriate biphosphonates therapy	In utero transplantation of adult bone marrow has been shown to decrease perinatal lethality in a murine model of osteogenesis imperfecta Rehabilitation and conservative care

Contd...

Condition	Medical	Surgical	Remarks
Achondroplasia	Somatotropin (recombinant human growth hormone) Most benefit during 1st year and when started at 1–6 years	• *Spinal canal stenosis*: Wide, multilevel laminectomies with foraminotomies. Extradural removal of herniated disc material. The length of decompression usually extends from the lower thoracic spine to the sacrum to prevent recurrence. Maintaining the integrity of facet joints is important to prevent postlaminectomy instability which may need anterior fusion • *Thoracolumbar kyphosis*: Observation for the child who has not begun to walk because spontaneous resolution occurs. Early prohibition of unsupported sitting If wedging of the apical vertebra persists after independent ambulation (typically wedging of 12th thoracic or 1st lumbar vertebra), an extension-type thoracolumbosacral orthosis should be used If the thoracolumbar kyphosis persists and measures greater than 30° at age 5 years, then surgery in the form of combined anterior and posterior fusion is performed. Posterior instrumentation generally is not recommended, due to the narrow canal size. Any instrumentation placed in the canal, such as hooks or sublaminar wires, is contraindicated due to the marked stenosis and decreased subarachnoid fluid space If kyphosis is associated with a neurologic deficit such as paraplegia, laminectomy alone is not indicated because it can destabilize the spine further. Treatment should consist of anterior cord decompression with strut grafting and posterior fusion • *Genu valgum*: Surgical correction of genu varum in the form of proximal tibiofibular osteotomy or proximal and distal fibular epiphysiodesis may be required Osteotomy is performed when rapid correction of symptomatic deformity is required. It can be performed through small incisions without internal fixation, with long-leg cast immobilization for 6 weeks • *Limb lengthening*: Limb lengthening of the upper and lower extremities is promoted in Europe but opposed by the Little People of America (LPA) and Dwarf Athletic Association of America (DAAA). If lengthening is to be performed, any existing angular deformities should be corrected simultaneously. With the current techniques of distraction osteogenesis, 30 cm of length can be gained. Gradual lengthening of the osteotomy callous (callostasis) or through the epiphyseal plates (chondrodiastasis) can be obtained using monolateral frames or Ilizarov ring fixators. The 6-segment lengthening (femur, tibia, humerus) can be performed as staged procedures in various sequences • *Foramen magnum decompression (neurosurgery)*: Narrowing of the foramen magnum may result in a variety of neurologic problems in the first several years of life. Significant improvement of severe neurologic symptoms has been reported with foramen magnum decompression and C1 laminectomy (*prophylactic surgery is not recommended*)	Services of following specialists may be needed: Geneticist for counseling and ascertaining the inheritance patter. Pulmonologists as they are at risk for sleep apnea Dental surgeon as malocclusion and overcrowding of teeth common. Obesity is common and dietary advice is important A potential exists for major complications during 6-segment lengthening. (Neurologic injury has been reported in 35% of procedures. Foot drop, vascular compromise, soft-tissue contractures, loss of motion, knee subluxation, infection, psychological changes, and death have been reported with extensive lengthening procedures)

Contd...

Condition	Medical	Surgical	Remarks
		• Ventriculoperitoneal shunts are indicated for patients with rapidly progressive head enlargement, increased intracranial pressures, or neurologic signs and symptoms	Neurosurgery is also indicated for other neurologic abnormalities, such as Chiari malformations
Cleidocranial dysplasia	Prevention of ear infection and its management. Hearing assessment at regular interval	No special management except for otitis media and dental corrections	Occasionally patients have large anterior fontanel requiring helmet wearing
Fibrodysplasia ossificans progressiva	No definitive treatment, but a brief 4-day course of high-dose corticosteroids, started within the first 24 hours of a flare-up, may help reduce the intense inflammation and tissue edema seen in the early stages of the disease Pamidronate has been useful in flare-ups. Palovarotene is a retinoic acid receptor Gamma (RARγ) agonist and is under trial	Oral pain management due to flare-ups involving jaw and mandibular area Most patients are wheelchair-bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome The importance of a minimally invasive surgical technique and appropriate anesthetic management has been stressed Patients should be protected from inappropriate surgical procedures, including biopsies if possible, to avoid harming them	Preventative management is based on prophylactic measures against falls, respiratory decline, and viral infections. The median lifespan is approximately 40 years of age

with rare bone disorders that are caused by mutations in single genes. Particularly important have been studies on OI. The widespread availability of advanced methods for DNA sequencing and bioinformatics analysis can be expected to greatly facilitate identification of novel gene networks that normally function to control bone formation and maintenance. Parallel advances in pathway analysis algorithms, together with open access to both chemical and pharmaceutical libraries, have for the first time enabled informed therapeutic targeting of disease causing gene pathways. Isolating the causative mutation of a disorder is essentially a bioinformatics—intensive logic puzzle, and choosing the right combination of individuals to sequence can be the key to solving it. For recessive conditions, Next generation sequencing (NGS) of an affected individual and their parents is an ideal design. Many common variants can be identified if their sequence is compared with closely related and even distantly related who are also affected. The details of molecular approaches for skeletal dysplasia are beyond the scope of this chapter.

MANAGEMENT

Many medical and surgical modalities have come up both for treatment of conditions as well as managing and preventing complications in skeletal dysplasia and have been summarized in **Table 7**. Readers can access relevant resources for details based on individual need of patients.

MORE ON THIS TOPIC

Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. J Clin Res Pediatr Endocrinol. 2011;3:163-78.

Byers PH, Krakow D, Nunes ME, Pepin M. Genetic evaluation of suspected osteogenesis imperfecta (OI). Genet Med. 2006;8:383-8.

Dighe M, Fligner G, Cheng E, et al. Fetal skeletal dysplasia: an approach to diagnosis with illustrative cases. Radiographics. 2008;28:1061-77.

Groza T, Hunter J, Zankl A. The bone dysplasia ontology: integrating genotype and phenotype information in the skeletal dysplasia domain. BMC Bioinformatics. 2012;13:50.

Krakow D, Rimoin DL. The skeletal dysplasia. Genet Med. 2010;12:327-41.

Lazarus S, Zankl A, Duncan EL. Next-generation sequencing: a frame shift in skeletal dysplasia gene discovery. Osteoporos Int. 2014;25:407-22.

Marini JC, Blissett AR. New genes in bone development: what's new in osteogenesis imperfecta. J Clin Endorinol Metab. 2013;98:3095-103.

Nampoothiri S, Yeshodharan D, Sainulabdin G, et al. Eight years' experience from a skeletal dysplasia referral center in a tertiary hospital in Southern India: a model for the diagnosis and treatment of rare diseases in a developing country. Am J Med Genet Part A. 2014;158:1-7.

Piga AM, Ferreira VA, Villaverde-Hueso A. Implications of the new etiopathogenic approach in the classification of constitutional and genetic bone diseases. Reumatol Clin. 2011;7:248-54.

Ravi K. Epidemiology of Handigodu syndrome among the Adi Karnataka Community of Karnataka. J Anth Survey India. 2011;60:1-18.

Warman ML, Vormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet Part A. 2011;155:943-68.

IN A NUTSHELL

1. Multiple attempts at classification of skeletal dysplasias and the fact the revision is occurring every 4th year shows that our understanding of skeletal dysplasias continues to evolve.

2. Short stature or deformed bones may provide the first clue for skeletal dysplasias but not always. The storage disorders are also being classified as a form of skeletal dysplasias.

3. Skeletal dysplasias may also presents with certain system manifestations like hearing deficit, hematological manifestation, neurological impairment or coarse features. Ever increasing list also proves their heterogeneity.

4. The molecular diagnosis of a skeletal dysplasia is both labor intensive and extremely cost-prohibitive currently because of their rarity. Availability of simple but specific markers may be helpful.

5. Antenatal diagnosis of a skeletal dysplasia through USG may be limited to very well defined dysplasia with severe manifestation. This poses a great challenge for clinician dealing with an uncomplicated pregnancy in the absence of a family history. Mild to moderate early onset skeletal dysplasias may not be even suspected on a routine USG.

6. If possible family members need to be convinced for a full pathological autopsy for an unexplained fetal death due to skeletal dysplasias. Otherwise a limited examination including photographs, radiographs, blood sample and skin biopsy may be helpful for a later study and counseling.

Chapter 49.11
Arthrogryposis
Jayanth Sundar Sampath, Harish S Hosalkar

Arthrogryposis is a term used to describe a clinical condition in which *congenital joint contractures affect two or more parts of the body*. It is a *clinical finding* rather than a specific disease. A search of the Online Mendelian Inheritance in Man (OMIM) database using the term *arthrogryposis* yielded 157 distinct genetic disorders with the *arthrogrypotic* phenotype, though some authors have classified more than 300 diseases as belonging to this group.

Individual disorders within this huge spectrum have varying etiology, clinical manifestation, natural history, prognosis and treatment. This has made it difficult to evolve a simple algorithmic or *cook book* approach to managing children with arthrogryposis. Nevertheless, many of the disorders share certain commonalities which can guide the clinician's efforts at rationally managing this difficult condition. The prevalence has been estimated at 1 in 3,000 livebirths.

CLASSIFICATION

Congenital contractures can be divided into two groups: *isolated contractures* (such as idiopathic clubfoot) or *multiple contractures* (represented by the arthrogrypotic syndromes).

Arthrogryposis can be further classified based on the neurological function of the child. If the neurological examination is normal, the possibilities include amyoplasia (also called arthrogryposis multiplex congenita), distal arthrogryposis, multiple pterygia syndrome, a generalized connective tissue disorder or fetal overcrowding. If the neurological examination is abnormal, causes include disorders of the central or peripheral nervous system, the neuromuscular junction or within the muscle.

CLINICAL FEATURES, DIAGNOSIS AND INVESTIGATIONS

Clinical features of the more common diseases within the arthrogryposis spectrum are discussed under their individual subheadings.

If typical clinical features are present, consultation from a clinical geneticist in conjunction with a pediatric orthopedic surgeon and pediatric neurologist can help with diagnosis and identification of specific subtype in individual cases. In other cases, a process of exclusion is adopted to narrow the possibilities to a particular category (central nervous system [CNS] disorder, spinal cord dysfunction, neuropathic, myopathic or unknown). In developing countries, many sophisticated genetic tests are not readily available and are usually expensive and therefore not feasible. The treating clinician should weigh the *pros and cons* of proceeding further with the diagnostic process. For instance, if there is a strong possibility of risk to future offsprings, the expense of a detailed genetic evaluation may be justified.

ARTHROGRYPOSIS MULTIPLEX CONGENITA

Arthrogryposis multiplex congenita (AMC) represents one of the more distinct forms of arthrogryposis and affected children exhibit typical clinical features. With his description of a *human monster with inwardly curved limbs* in 1841, Adolf Wilhelm Otto from the Anatomical Museum in Breslau is credited with the first description of an infant with arthrogryposis. The term AMC was coined by Stern (1923) and the name *amyoplasia* was later given by Sheldon in 1932.

Epidemiology and Etiopathogenesis

The condition is sporadic with an equal sex distribution. Identical twins are discordantly affected, indicating that an abnormal intrauterine environment or the twinning process itself may be contributory. Teratogens are known to cause congenital contractures in animal models, though this is yet to be proven in humans. Maternal antibodies to the fetal acetylcholine receptor have been implicated in the causation of amyoplasia. Reduced number of anterior horn cells in the spinal cord has been noted, corresponding to the muscles affected and pattern of contractures. An in utero disturbance of CNS development may therefore be important.

In relation to pathogenesis of the arthrogryposis spectrum, Hall (1986) stated: "The *use* of a structure in utero is necessary for its continuing and normal development. The old adage *use it or lose it* seems to apply just as appropriately to prenatal normal development as it does in the crusty adult world of politics, business, and academia."

Clinical Features

Arthrogryposis multiplex congenita remains a clinical diagnosis. The appearance and position of the extremities are characteristic. The limbs appear tubular and featureless, lacking the usual flexion creases at the elbow, wrists and knees. Deep dimples may be seen, particularly over the anterior aspect of the knee. Muscle mass is reduced, typically resulting in lack of contours to the shoulders and thin stick-line calves. In infants, there is an abundance of subcutaneous fat which is freely mobile over the markedly atrophic muscle groups. If the condition is diagnosed prenatally (as a consequence of reduced fetal mobility and the presence of contractures or deformity), elective cesarean section is usually performed. During vaginal delivery, fractures of the femur or other long bones can occur. There is reduced movement in several joints with a firm block beyond a limited range.

Feeding, swallowing and respiratory difficulties may be encountered in the neonatal period necessitating supportive treatment. Jaw stiffness, an immobile tongue, hypo/retrognathia, a small jaw and weak respiratory muscles may together contribute to the above. A midline frontal hemangioma is sometimes present.

The shoulders are adducted and internally rotated, the elbow joints extended and the wrists in severe flexion and ulnar deviation. The fingers are variably affected with some joints in flexion and others in extension. A *thumb-in-palm* deformity is seen in many infants.

The hips typically rest in a position of flexion, abduction and external rotation. The knees are stiff in extension, though flexion contractures may develop as the child becomes older. Severe knee flexion contractures at birth are more characteristic of the congenital pterygium syndromes than classic arthrogryposis. The most common foot deformity is a stiff and severe clubfoot (congenital talipes equinovarus [CTEV]) which is resistant to manipulation. Less frequent are a stiff variety of calcaneovalgus deformity or a *rocker bottom foot* (congenital vertical talus) **(Figs 1 to 4)**.

Visceral anomalies are relatively rare in AMC. An ultrasound of the abdomen is a simple, noninvasive way of confirming this. Inguinal hernias can occur in up to 15% of individuals owing to generalized muscle weakness. Language development may be delayed due to weakness of the tongue and muscles of speech.

Figure 1 Arthrogryposis with right rocker bottom foot, left clubfoot, and bilateral congenital knee dislocation

Figure 2 Older child with arthrogryposis multiplex congenita. Note lack of creases in the joints, tubular legs, bilateral knee extension contractures and rocker bottom feet

Figure 3 Arthrogryposis multiplex congenita with severe knee flexion contracture and bilateral clubfoot

Figure 4 Arthrogryposis multiplex congenita with bilateral developmental dysplasia of the hip

Intelligence is normal and most children demonstrate remarkable abilities to adapt to their environment in the face of severe physical impairment.

Treatment

The management of children with AMC is difficult and a multidisciplinary approach is warranted. Long-term treatment decisions should take into account the severity of the condition, natural history and anticipated functional status at maturity.

A study of eleven individuals with AMC who were followed from birth to maturity suggests that the ambulatory status of many children could be improved by adopting an early aggressive approach to the management of muscle strength, joint dislocations and contractures. Severity of the disease at birth did not correlate with function at maturity, though almost all children who were eventual independent ambulators had walked by the age of 2½ years.

Close coordination between the physical therapist, occupational therapist and pediatric orthopedic surgeon is necessary throughout childhood. Judicious, well-timed surgical intervention along with serial casting, muscle strengthening exercises, night-time splinting of joints and day-time use of orthotics remain the mainstay of treatment.

Hip dislocation can be unilateral or bilateral and is present in two-thirds of patients. The diagnosis must be made soon after birth. Conservative management in a Pavlik harness or hip abduction brace is ineffective in most cases as is closed reduction of the dislocated hip. Staheli et al. pioneered the medial open reduction for dislocated hips in AMC, an approach now adopted by many centers. This procedure is carried out through a minimally invasive approach with a reduced period of immobilization (typically around 8–12 weeks in a hip spica). Current opinion favors reducing dislocated hips at approximately 4–6 months of age in most children with AMC for unilateral and bilateral dislocations.

Knee extension contractures or a frank dislocation of the knee is typical of AMC at birth. Flexion contractures may be present at birth or develop later in life with growth. Serial casting and regular stretching exercises by trained therapist/parents is attempted soon after birth but is successful in a small number of cases. In babies who are unresponsive to nonsurgical treatment, elongation

of the quadriceps tendon by a percutaneous tenotomy or formal Z-lengthening may be required. Where necessary, the surgery can be conveniently timed with open reduction of the hip. Neglected knee extension or flexion contractures can affect ambulatory potential and are best dealt with before the first year of life. Several contracture releases or bony procedures may be required throughout childhood, as recurrences are common. A child with AMC may undergo as many as ten procedures in order to maintain independent ambulation.

Rigid clubfeet are the rule in children with AMC. Ponseti method is the current gold standard for the management of clubfoot. Several authors have reported good initial success rates with Ponseti method in rigid clubfeet. Treatment of the clubfoot is commenced soon after birth with serial casting followed by a percutaneous achilles tenotomy. A strict regime of full-time (for 3 months), followed by night-time use of foot abduction braces up to the age of at least 4–5 years is recommended. Recurrences are common and follow-up surgery may be required in 30–40% of cases. Radical bony procedures such as talectomy (surgical removal of the talus) were commonly performed in the past for stiff clubfeet in AMC. With the advent of Ponseti method, the need for radical bony procedures in young children may be avoided.

Most patients may not require surgery to the upper limb. Many children adapt very well even in the presence of severe contractures. A detailed functional assessment by an occupational therapist and the opinion of the parents are important components of the decision making process. Typical procedures include humeral osteotomy to improve flexion at the elbow, dorsal wedge carpectomy to place the wrist in a neutral position and release of a *thumb-in-palm* deformity.

Scoliosis is present in approximately 33% cases. Surgical correction is reserved for progressive, severe curves that interfere with sitting balance or walking potential.

IN A NUTSHELL

1. Arthrogryposis refers to a clinical picture, where congenital joint contractures involve two or more parts of the body. This group includes more than 300 conditions.
2. Arthrogryposis multiplex congenita (AMC) belongs to a spectrum of multiple congenital contracture syndromes of varying etiology.
3. Diagnosis is typically made on the basis of characteristic clinical features.
4. Orthopedic management is complex and should be attempted in a multidisciplinary setting.

MORE ON THIS TOPIC

Arthrogryposis multiplex congenita. Br Med J (Clin Res Ed). 1981;283:2-3.

Eckel EM. Arthrogryposis multiplex congenita. Phys Ther. 1970;50:665-9.

Hosalkar HS, Moroz L, Drummond DS, Finkel RS. Neuromuscular disorders of infancy and childhood and arthrogryposis. In: Dormans JP. Pediatric Orthopaedics: Core Knowledge in Orthopaedics. Philadelphia: Elsevier Mosby; 2005.

Hosalkar HS, Drummond DS, Davidson RS. Arthrogryposis. In: Kliegman RM, Stanton BF, St. Geme JW, et al. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier; 2011.

Laitinen O, Hirvensalo M. Arthrogryposis multiplex congenita. Ann Paediatr Fenn. 1966;12:133-8.

Symposium: Arthrogryposis multiplex congenita. Clin Orthop Relat Res. 1985;194:1-123.

PART IX Child in the Social Milieu

Section 50 VULNERABLE CHILDREN

Section Editor *Sanjay Chaturvedi*

Chapter 50.1

Vulnerability

Dheeraj Shah, Piyush Gupta

The concept *vulnerability* refers to groups of children that have a high probability of negative outcomes—such as the loss of their education, morbidity, and malnutrition—at higher rates than do their peers (World Bank: *Orphans and Vulnerable Children (OVC)* toolkit). This would include vulnerability to deprivation (food, education and parental care), exploitation, abuse, neglect, violence, and illnesses. The context of vulnerability, however, varies over time and place. According to World Bank, *vulnerability is a relative state—a multifaceted continuum between resilience and absolute helplessness*. It outlines the following main categories of vulnerable children: (*i*) street children, (*ii*) children in the worst forms of child labor, (*iii*) children affected by armed conflict, (*iv*) children with chronic illness, (*v*) orphans, and (*vi*) children living with disability. A vulnerable child can be grouped into more than one of these categories; orphans can also be street children or having disability. Some specific indicators for vulnerability are summarized in **Box 1**.

Family situations that make the child vulnerable Parental discord, disharmony, divorce, drug abuse, addiction, and alcoholism are important risk factors. Children are likely to be vulnerable, if one or both parents are physically or mentally handicapped or seriously ill.

BOX 1 Indicators of vulnerability for children

- Any physical or mental handicap or any other long-term difficulty that would make it difficult for the child to function independently;
- Illness, either HIV or other major illness;
- Emotional or psychological problems;
- Abuse at emotional, physical or sexual level;
- Not cheerful, dull, does not perform well in class, miserable, dirty with torn or inadequate clothes, sleepy;
- Use of drugs, e.g., glue, alcohol, cigarettes, cannabis, cocaine;
- Neglect of schoolwork, does not attend school regularly, does not perform well at school;
- Does not receive sufficient healthy food and constantly shows signs of hunger;
- Poor hygiene or cannot engage in personal care;
- Does not receive care, particularly love, guidance and support.

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Poor and crowded household, and lack of time by the caregivers for guidance and direction to children also make a child vulnerable.

The community context Children living in dangerous situations, with exposure to war, crime, abuse, poverty are more likely to be vulnerable. Lack of proper schooling, play, and living in settlements with poor water, housing and sanitation facilities also prevent the child from leading a normal life.

BURDEN OF VULNERABLE YOUNG PEOPLE

According to UNAIDS-UNICEF-USAID estimates, India houses about 40% of the total orphaned children in Asia. There were 35 million children (age 0–18) orphaned due to all causes in 2003 in India, and orphans constituted about 9% of the total children. Out of these, 15.7 million were maternal orphans and 23.3 million were paternal orphans. Four million children had lost both their parents (double orphans). The projections for 2010 were 32.3 million comprising 8% of total childhood population. Direct estimates for orphan young people are not available but the general trends from other regions suggest that more than half of the orphans are aged more than 12 years.

Extreme poverty is another potential situation of vulnerability. According to UNICEF estimates, 42% of India's population lives below international poverty line of USD 1.25 per day. According to a report released by Planning Commission of India in 2013, 25.7% of rural and 13.7% of urban population of India lives below the poverty line of INR 816 and 1,000 per month, respectively.

Early marriage and childbirth make a young female vulnerable to malnutrition and domestic violence. In India, early marriage and childbirth is a very common phenomenon. According to NFHS-3 survey, 27% of girls aged 15–19 years were currently married, and more than one out of five (22%) married women (aged 20–24 years) gave birth before attaining the age of 18 years.

INTERVENTIONS TO MODIFY VULNERABILITY

In view of the lack of a uniform definition of vulnerability, and multiple factors producing a potentially vulnerable situation in children, it is difficult to assess the impact of interventions on modifying vulnerability. There is no Indian data regarding the impact of any single intervention or a package of interventions on the factors constituting vulnerability. Most available data relate to the prevalence and factors related to alcohol or smoking or substance abuse.

Some other studies have focused on school-based programs to modify the risk of substance abuse and violence. In general, school-based programs, especially those targeted towards high-risk students, and those involving skilled personnel and peer leaders had a moderate impact in modifying the outcomes.

CONCLUSION

The concept of vulnerability generally refers to the groups of people who are more exposed to risks than their peers. Vulnerability is a relative state with its degree and type varying overtime and between countries, and is highly contextual. Children and young people separated from their parents are clearly vulnerable groups. Besides that, extreme poverty, chronic illness—of self or parents—and lack of social support and education also make children vulnerable to abuse, neglect, deprivation and violence. Indian data regarding *what constitutes vulnerability* in adolescents or young people are lacking. Efforts must be directed to identify and quantify the most vulnerable sections of the society to effectively target the remedial interventions.

MORE ON THIS TOPIC

Andrews G, Skinner D, Zuma K. Epidemiology of health and vulnerability among children orphaned and made vulnerable by HIV/AIDS in sub-Saharan Africa. AIDS Care. 2006;18:269-76.

Skinner D, Tsheko N, Mtero-Munyati S, et al. Towards a definition of orphaned and vulnerable children. AIDS Behav. 2006;10:619-26.

Smart RA. Policies for Orphans and Vulnerable Children: A Framework for Moving Ahead. USAID, 2003.

UNICEF. Child Protection from Violence, Exploitation and Abuse—Orphans and Vulnerable Children, 2010. Available from: http://www.unicef.org/protection/index_orphans.html. Accessed July 1, 2014.

World Bank. OVC Core Definitions. Available from: http://info.worldbank.org/etools/docs/library/164047/howknow/definitions.htm. Accessed July 1, 2014.

IN A NUTSHELL

1. The factors deciding vulnerability are complex and cross-cutting: can be grouped into material problems, emotional problems, and social problems.
2. Street children, those engaged in child labor, orphans, disabled children and those with chronic illnesses are usually considered vulnerable.
3. Loss of one or both parents, chronic illness of self or parents, and extreme poverty constitutes a widely accepted situation of vulnerability.
4. Female gender increases vulnerability to sexual violence whereas males are more vulnerable to other forms of violence.
5. There is an urgent need to conduct country specific research to define vulnerability and estimate its burden in Indian context.
6. There is a paucity of information related to interventions that can reduce or minimize vulnerability to abuse, violence, exploitation, neglect or deprivation.
7. Targeted school-based programs are effective at curtailing vulnerability, substance abuse and violence.

Chapter 50.2
Street Children
Pranab Chatterjee, Sanjay Chaturvedi

"Being poor is in itself a health hazard; worse, however, is being urban and poor. Much worse is being poor, urban, and a child. But worst of all is being a street child in an urban environment."

—de la Barra, X *(Poverty: the main cause of ill health in urban children. Health Educ Behav. 1998;25:46-59).*

Who are Street Children?

There has been much disagreement about the definition of street children, which has led to a lot of issues in enumeration and policy-making. Though the most commonly accepted definition of a *child* is adopted from the United Nations Child Rights Convention, which sets the cut-off at 18 years, Indian law has a different interpretation, which causes some operational difficulties. Article 24 of the Indian Constitution, the Child Labor (Prohibition and Regulation) Act of 1986 and Section 2(c) of The Factories Act of 1948 (amended 1987) all lay down the fact that a child is anyone who has not completed 15 years of age.

Additionally, there is some disagreement about what constitutes a *street child* as well. UNICEF defines a street child as "*...any boy or girl for whom the street (in the widest sense of the word, including unoccupied buildings, wastelands, etc.) has become his or her habitual abode and/or source of livelihood; and who is inadequately protected, supervised or directed by responsible adults".* These children have been further classified as *children of the street* or *children on the street. Children of the street* are homeless, working children, who live on the streets, while *children on the street* are poor, working children, who spend a large portion of the day, living and working on the streets, but who see their families regularly and usually return to their families at night. Some social scientists have defined street children in the light of their behavioral attributes. Cosgrove, who belongs to this school, defined street children as "*any individual under the age of majority whose behavior is predominantly at variance with the community norms, and whose primary support for his/her development needs is not a family or a family substitute".*

Several experts are of the opinion that the very term *street children* is problematic. Emerging evidence asserts that instead of focusing on the term *street child*, it is more prudent to focus on both the categories of *children on the street* and *children of the street,* since this also encompasses the poor, working children, who live with their families, but still are in need of protection and welfare. **Box 1** highlights the shortcomings of the term *street child*.

BOX 1 Problems with the term *street children*

1. A generic term obscuring the heterogeneity of the children's circumstances of being on the street.
2. Children move on and off the street; a rigid classification precludes understanding of this fluid change of status.
3. May be interpreted to convey a derogatory or pity-inducing connotation.
4. Deviates attention from the more striking problem of children affected by poverty and social exclusion.
5. May reflect a social-political agenda, is difficult to translate into an operational concept as evinced by conflicting evidence.
6. The *on the street/of the street* dichotomy is an over-simplification that is defied by the behavior of the children, who may sleep both at home and on streets, or even in shelters or other institutions.

Epidemiology: The Problem Statement

Although no official statistics are available, estimates peg the number of street children globally anywhere between 10 million and 100 million. This is a reflection of the discrepancies arising out of the conflicting definition of a street child. The Asian Development Bank put the number of street children in Asia at 25 million. Workers in India widely believe in an estimate putting the number at 400,000–800,000. In the Latin American countries, the number of street children is put at about 40 million. Most street children are aged between 5 years and 17 years, with the UNICEF estimating that 72% of them are aged 6–12 years. In India, the National Institute of Urban Affairs put the mean age of street children at 13 years in 1989.

One trend that has been observed uniformly in the developing countries is that a majority of the street children are boys. The fact that in the developed countries street children do not have a gender preponderance has led to discussions on the differential etiology of homelessness in different settings. Girls, though difficult to trace, and part of a numerical minority, are, however, more vulnerable. On the surface, this is contrary to the usual finding that it is the female child who is likely to face more oppression and neglect at home. One claim that has found some supporters is that the girls are taken off the streets to be put into prostitution. Another school of thought reckons that though this is a possible scenario, it is more likely that boys are actually more numerous on the streets. Girls contribute to the household work, and are culturally less likely to leave home than boys are. The step-parent/step-child dynamic is also more likely to push boys out into the streets than girls. Most street children come from matrifocal families—a setting in which the boys are more likely to start acting as breadwinners while girls are held back at home.

Another emerging trend has been that political unrest pushes children out into the streets. Comparative analysis of street child ethnography from mid-19th century Ireland and current Sudan has incriminated civil unrest to be a contributing factor for a spike in the number of street children.

All said and done, being a street child is a relatively modern, mostly urban phenomenon, which implicates that areas with a strong indigenous cultural trend are less likely to suffer from this problem. Social scientists have established this hypothesis in Latin America, where they compared the street children phenomenon in Guatemala City, and Bogota, and showed that the westernized, urbanizing influence in Bogota was associated with a higher number of street children.

Etiology: Why do Children Move onto the Streets?

The predominant reasons pushing children out into the streets vary from one setting to another. Though multiple reasons have been held responsible for the emergence of street children as a public health problem, four overarching themes have been identified: urbanization, urban poverty, aberrant family structure and medical reasons. **Box 2** identifies some key components of each of these themes.

However, not all countries share the same issues. In the developed world, males and females are equally represented on the streets. This has been postulated to be due to the fact that the developed world street children originate from aberrant families, which are likely to affect both the genders equally. In African countries, a major segment of the street children have been driven out of home either due to civil unrest, political instability or the ravages of the AIDS pandemic. In the Latin American nations, urban poverty is the major factor. Although parental abandonment has long been thought to be the bane of Latin American nations, research by Mark Lusk has shown that the Latin American children

| BOX 2 | Etiologic understanding of the street child phenomenon |

- *Urbanization:* Disintegration of the traditional way of life
  - Attraction to the city way of life
  - Attrition of the conventional family structure with loss of a strong community support
  - Industrial or service economy booming at the cost of agrarian economy
- *Urban poverty:* Economic pressure and demand-supply mismatch
  - Abandonment of children by poor families
  - Pushing children out to earn
  - Lack of adult employment opportunities
  - Poor social security and support system
  - Civil unrest
  - Lack of political will
- *Aberrant family:* Street children are more likely to come from broken or female-headed families
  - Death of either/both parents
  - Paternal alcoholism
  - Strained relationship with step-parents
  - Parental abuse
  - Parental separation
  - Family violence
- *Medical causes:*
  - AIDS-related deaths of young parents
  - Mental health issues leading to abandonment or runaways
  - Antisocial behaviors or recidivistic criminal behavior

Figure 1 Graphically depicts a theoretical framework for a qualitative understanding of the vulnerability of street children based on various attributes. The size of the different circles represents the vulnerability levels for each of the groups mentioned, a larger size indicating a higher level of vulnerability. The various groups are: A (poor working children returning home at night); B (independent street working children whose family ties are beginning to disintegrate); C (children of street families, living and working on streets); D (children who have broken off all family ties)

"*are on the streets to work and earn money because there is not enough at home*". In India, however, the etiology is different. A few studies have shown that the main reason for children being driven out into the streets is not urban poverty as has been long believed, but family discord and abuse.

Social Pathogenesis: The Making of a Street Child

Building up on the work of Mark Lusk, it is clear that most children are driven into the streets gradually. Lusk enumerated four categories of street children, which we can combine with the concepts of Cosgrove to arrive at a qualitative understanding of vulnerability to map the social pathogenesis of a street child. Lusk's four categories were:

A. Poor working children who returned to their families at night; they are more likely to attend school, and have less delinquent behavioral traits.
B. Independent street workers, whose family ties are beginning to break, with a concomitant reduction in school attendance and increased delinquent proclivities.
C. Children of street families, living and working on the streets; they have stronger family ties but are unlikely to have good school attendance, have delinquent propensities and are more likely to suffer from poverty-related issues.
D. Children who have broken off family ties completely.

These categories can be viewed as incremental stages of dissociation from the family and recession into a street life. Combining these stages with Cosgrove's characterization of street children based on the dimensions of degree of family involvement and amount of deviant behavior, we can arrive at a qualitative understanding of the level of vulnerability for each category. This helps us map the different groups in an ascending order of likelihood to stay on the streets. **Figure 1** graphically represents how these determinants can be used, in combination with an understanding of their vulnerability, to pictorially chart out the route a child may take from high family ties, low vulnerability, settled situation to a low family ties, high vulnerability, street-living situation.

Health of Street Children

Street children suffer from a multitude of conditions arising from neglect and poverty. The major health issues include a wide spectrum of conditions like poor nutrition, trauma and injuries, skin-related infections (especially scabies and pyoderma), respiratory infections (like tuberculosis, viral infections), gastrointestinal infections (including diarrhea, worm infestations), drug abuse (smoking, alcohol and glue sniffing or inhalant abuse), to name a few. Street children are also especially susceptible to sexually transmitted infections as they initiate sexual activity at a very early age. Survival sex, commercial sex work, and group sex make them especially prone to develop sexually transmitted infections. Some NGOs have reported that the prevalence of HIV in street children of Delhi is as high as 6%, while that of other sexually transmitted diseases may be to the tune of 2–3%.

Street children may also act as an occult, bridging population for HIV infections, especially considering the fact that they also indulge in IV drug use with shared needles, and commonly have unprotected sex. Since the public health programs do not generally cover street children, they escape the checks in place and act as a continuing source of disease propagation. This is of grave importance given the large number of children on the streets of urban India.

These children also suffer from a number of mental illnesses, including, but not limited to, poor self-esteem, discipline issues, antisocial behavior, personality disorders, and maladaptive coping mechanisms. Street children develop coping mechanisms to deal with the harsh life on streets. These strategies include the development of a tough exterior, strong independence, constantly living in survival mode, and being aware to fight for safety. They are forced to adopt behavioral patterns that children living with housed families do not need to. Some of these coping mechanisms are highlighted in **Box 3**.

BOX 3 Coping mechanisms used by street children

A. *Positive coping mechanisms:*
1. Adoption of surrogate families or family substitutes
2. Living in groups
3. Emotional engagement with peer groups
4. Emotional resilience

B. *Maladaptive coping mechanisms:*
1. Alcohol abuse, smoking, inhalant abuse, drug abuse
2. Adopting negative behavioral traits for peer group acceptance
3. Commercial or casual or survival sex.

Although it sounds unlikely, but in certain situations being a street child may not always be a detrimental fate. In settings where children are pushed out of their homes due to poverty and financial pressures, studies have found that working, street children are likely to fare better than housed, poor, working children. A large study of 1,000 children in Tegucigalpa, Honduras established this by showing that street children had significantly better nutritional status than their housed peers. Some experts support this counter argument **(Box 4)** especially in groups exhibiting resilience and positive coping mechanisms.

Another issue related to the health of street children, is their health-seeking behavior, or rather, the lack of it **(Box 5)**. On one hand, multiple reasons predispose street children to be hesitant in seeking out health care services, while on the other, the conventional system is tentative in dealing with this unconventional group of patients.

Management of Issues Related to Street Children

The WHO has a special project on street children that incorporates prevention of substance abuse (WHO/PSA) program. Using the model of the WHO Program on Prevention of Substance Abuse, a systematic approach can be developed to deal with the issues of street children. Such a model would not be a generic answer, but, rather, act as a template that could be adopted and modified to provide a local solution, since the issue of street children is largely culturally modulated. **Box 6** highlights the key strategies of this model.

BOX 4 A counter perspective: Street children may not be worse off

"Rather than being the most victimized, the most destitute, the most psychologically vulnerable group of children, street children may be resilient and display creative coping strategies for growing up in difficult environments."

—Veale A, Taylor M, Linchan C. Psychological perspectives of 'abandoned' and 'abandoning' children. *In:* Panter-Brick C, Smith MT, editors. Abandoned Children. Cambridge, UK: Cambridge University Press; 2000. pp. 131-45.

BOX 5 Health-seeking behavior of street children

1. Street children view conventional health-care system as unhelpful, inaccessible, unaffordable, unfriendly, and regard health-care professionals with suspicion—may be a part of the natural coping mechanism.
2. An overburdened and rigid health-care system that is not malleable to accommodate the special demands placed by these children experiencing harsh circumstances.
3. Lack of empathy, and an impersonal service provider may further alienate these children, who view everyone outside their safety circle with suspicion.
4. Health-care providers may worry about issues of consent and compliance while treating unaccompanied minors, especially in critical cases with unpredictable or unfavorable outcomes.
5. Drug-seeking behavior of drug-using children may modulate treatment or prescribing decisions.

BOX 6 Strategies of a community-based approach to street children

1. The model should be implemented keeping in mind the cultural compulsions, and community expectations. Street children should be stakeholders in the decisions about their future.
2. *Street education* should be the cornerstone of the program. This focuses on counseling about harmful effects of substances, prevention of STDs, improvement of literacy rates, improved health seeking behavior, life skills training, and vocational training.
3. Utilize NGO/street-based clinics as a liaison between street children and conventional health-care system.
4. Improve accessibility, affordability, and acceptability of conventional health-care service providers, rather than create de novo a parallel system to cater to this niche population.
5. Move for inclusive growth at the community level, and on the larger scale, at the national level.
6. Organized rehabilitation should be supplemented by active advocacy to raise awareness and funds.

EARLY INTERVENTION AND REPATRIATION PROGRAMS: THE INDIAN STORY

Several NGOs, in collaboration with the Ministry of Women and Child Development (WCD), have worked towards implementation of an integrated program for street children. The major components of this program, as outlined by the Ministry, are summarized in **Box 7**.

This program, however, concentrates more on the runaway or abandoned street child and not poor, working children as a whole. Thus, these initiatives have fallen prey to the exclusive definitions of street children, taking cognizance of the problems of only one part of the whole group of children living a life of extreme vulnerability.

The program has the following goals and objectives:

Goals
- Provide a safer environment and improve the quality of life for children living and working on the streets.
- Early intervention for repatriation of runaway or abandoned children with their families.

BOX 7 Components of the Integrated Program for Street Children in India (Ministry of Women and Child Development)

- City-level surveys to generate locally-applicable evidence.
- Documentation of existing facilities and creation of a local, city-based, plan of action.
- Programs offering counseling, guidance and referral services brought under the ambit of the program.
- Create drop-in-centers working around the clock.
- Establish nonformal education programs at shelters and drop-in-centers.
- Establish program for reintegration of children with their families and place orphans or those unsuitable for reintegration in foster homes or residences.
- Enrolment of street children in schools.
- Enrolment of shelter/drop-in-center-visiting children in vocational training programs.
- Occupational rehabilitation.
- Introduction of street children as beneficiaries of public and preventive health services.
- Enrolment of street children in rehabilitation programs.
- Expansion of integrated child development services (ICDS) to include children on the street and children of the street as program beneficiaries.
- Post-ICDS program for nutritional rehabilitation of street children older than 6 years.
- Capacity building of service providers, advocacy to raise awareness and funds to support children on the street and children of the street.

Objectives

- Early identification of street children at railway stations, bus terminals, and market places.
- Informal counseling and motivation to increase utilization of drop-in-centers.
- Provide multiple services at the drop-in-centers to facilitate neurobehavioral development of the child while utilizing the facilities.

Repatriation is a key element of this integrated program and has the following components:

- Ascertainment of the willingness of the child for being reunited with the family.
- Family visits by trained staff to understand reasons behind the child being pushed out of home.
- Follow-up home visits to ensure smooth transition of children back into a family life and mitigation of factors responsible for pushing them out onto the streets.
- Children who cannot be reintegrated with their original families should be provided with education, food and shelter, health and psychosocial counseling, vocational and life skills training, and a chance at a stable life in a foster home.

General Recommendations to Address the Issues Affecting the Street Children of India

- Provision and protection of basic child rights as outlined in the United Nations Convention on Child Rights, especially, ensuring that every child has the right to education, health care (preventive, promotive and curative services), and opportunities to develop. This should be bolstered with abolition of child labor with stringent implementation of legal provisions. Traditionally, greater focus has been on the fulfillment of child needs as determined by the policy-making adults; the focus needs to shift from paternalistic fulfilling perceived child needs to assured provision of inalienable rights (see comment in **Box 8**).
- Establish the requisite number of drop-in-centers and shelter homes with adequate trained staff to ensure smooth functioning. There should be periodic assessment to assure quality performance by the functionaries.
- Multisectoral approach for a multidisciplinary problem: bring together community and NGO participation, child and social welfare systems, peer networks, health care activists, law and order system, and government initiatives to act in a coordinated manner.
- Expansion of childline and child protective services on a national level, and then expand it in phases, based on pilot project experiences.
- Develop a cadre of counselors and social workers to ensure psychosocial rehabilitation of abused children.
- Fulfill the provisions of the Juvenile Justice Act of 2000 and create a Juvenile Justice Board and Child Welfare Committee in every district of the nation.

BOX 8 From child *needs* to child *rights*

"In recent years, the entire concept of childhood has been reconstructed… Children are citizens…The idea that they are simply immature creatures whose needs must be met by parents or other charitably inclined adults is becoming obsolete. As citizens, children have rights that entitle them to the resources required to protect and promote their development."
—Earls F, Carlson M. Children at the margins of society: research and practice. New Dir Child Adolesc Dev.1999;85:71-82. PubMed PMID: 10750534.

MORE ON THIS TOPIC

Aptekar L. Street children in the developing world: a review of their condition. Cross Cult Res.1994;28:195-224.

Bhaskaran R, Mehta B. Surviving the streets: A census of street children in Delhi. New Delhi: Save the Children; 2011. Available from: http://resourcecentre.savethechildren.se/sites/default/files/documents/5332.pdf. Accessed June 7, 2014.

Consortium for Street Children. Available from: http://streetchildren.org. Accessed June 5, 2014.

Cosgrove JG. Towards a working definition of street children. Int Soc Work.1990;33:185-92.

le Roux J, Smith C. Causes and characteristics of the street child phenomenon: a global perspective. Adolescence.1998;33:683-8.

Lusk MW. Street children of Rio de Janeiro. Int Soc Work.1992;35:293-305.

The WHO Special Project on Street Children. Available from: http://www.who.int/substance_abuse/activities/street_children/en/. Accessed June 5, 2014.

UNESCO. Working with Street Children: Selected Case Studies from Africa, Asia and Latin America. Paris: UNESCO; 1995.

UNICEF. Children in especially difficult circumstances: Supporting annex, exploitation of working and street children. New York: United Nations Children's Fund; 1986.

UNICEF. Implementation Handbook for the Convention on the Rights of the Child. New York/Geneva: United Nations Children's Fund; 1998.

UNICEF. State of the World's Children. New York: United Nations Children's Fund; 2012.

IN A NUTSHELL

1. The definition of street children has been considerably debated. The most accepted version classifies them as *children on the street* (those who work on the streets but return to their families at night) and *children of the street* (those for whom the streets have become the homes and sources of livelihood).
2. There is wide disagreement about the exact number of street children. The estimated global tally of street children is between 10 million and 100 million, with 40 million of them being in the Latin American countries, and 25 million in Asia. India accounts for 400,000–800,000 street children.
3. Most street children are boys, aged 6–12 years, and originally from matrifocal families.
4. Four major themes underlie the etiologic considerations for children being pushed out of their homes: urbanization, urban poverty, aberrant families, and medical causes.
5. The process by which a poor, working-family child is pushed out into the streets is a gradual process, comprising of four sequential stages.
6. Street children are more likely to suffer from a number of medical conditions, usually resulting from poverty or neglect. Poor nutrition, trauma and injuries, infectious diseases, especially sexually transmitted diseases, are the most common afflictions.
7. Street children adopt multiple coping strategies to deal with the harsh street life. Some maladaptive coping strategies include alcohol, tobacco and drug use; and group, commercial, and survival sex.
8. Some studies have suggested that children living and working on the streets may enjoy a better health profile than their housed, poor, working peers.
9. Street children avoid contact with the conventional health care system, and regard it with considerable suspicion and scorn.
10. An Integrated Program for Street Children has been envisioned in India, the main focus of which is early identification, intervention, and repatriation of street children with their estranged families.

Chapter 50.3
Child Labor
SR Banerjee

Child labor is pervasive problem throughout the world, especially in developing countries. India has the largest number of child labor in the world and constituted around 3.7% of the total labor force. Majority of them (75%) work in rural settings and one-third are girls. But the alarming feature of the problem in recent years was the enormous increase of child workers in urban settings, especially in various types of work situations in unorganized urban sector. The children work the longest hours and are worse paid of all the laborers. They endure work conditions which include health hazards and potential abuse. As a result these children are deprived of their right to childhood, and are relegated to a life of drudgery.

HISTORICAL BACKGROUND

Child labor has a long history. From the ancient times, children have been working in agriculture and as apprentices to artisans. Child labor underwent major expansion and restructuring during the 1700s as a consequence of the need created by the industrial revolution for large number of workers. In that era, mill owners preferred to have children as workforce rather than adults. Children, as young as 11 years, especially girls, were sent to work in the mills by their families because the wages they could earn far exceeded the income of their parents working in their rural farms. Thus, in the preindustrial revolution period, the phenomenon of child labor was prevalent all over the world though having a different nature and magnitude altogether.

During the postindustrial period, the child labor became a growing phenomenon which is continuing to grow in developing countries. As in the West, child labor is not a new phenomenon in India. In India, child labor was identified as a major problem as early as 19th century and children were employed in cotton or jute mills and coal mines. As early as 1881, during the British period, legislative measures for the protection of child workers employed in hazardous jobs were adopted. Inspite of protective legislation, the social evils of child labor persisted in India from the early days of industrial period.

DEFINITION OF CHILD LABOR

According to encyclopedia of Social Sciences (1959) child labor was defined as: *"When the business of wage earnings or of participation in self of family support conflicts directly or indirectly with the business of growth and education the result is child labor".*

In the literature on child labor, different concepts such as *child work* and *child labor* are used synonymously. This creates confusion in the analysis of the problem of child labor and, therefore, affects the process of formulation and implementation of protective, legislative and action-oriented rehabilitation policies. The problem is also compounded by differences in social and cultural perceptions. The dictionary meaning of *worker* is an employee especially in manual or industrial work, while *laborer* is one, who, for wages does work that requires strength and patience rather than skill or training. Moreover, all work is not bad for children especially when the work is simple and properly structured and phased. This implies that the work which does not detract from other essential activities of children such as leisure, play or education is not child labor. Child labor, therefore, is the work which involves some degree of exploitation, i.e., physical, mental and social as the young children are physically, psychologically and mentally fully not matured and their physiological processes and reflexes are still undergoing development. This refers to economic exploitation in terms of low wages and physical and mental exploitation in terms of long hours of work, hazardous working condition, and lack of health-care, schooling and recreational facilities which ultimately threaten the health and overall development of children.

UNICEF has given comprehensive formulation in its attempt at defining the child labor:
- Starting full time work at too early an age
- Working too long within or outside the family so that children are unable to attend school
- Work resulting in excessive physical and psychological strength
- Work and life on the street in unhealthy conditions
- Inadequate remuneration for working outside the family
- Too much responsibility at too early an age
- Work that does not facilitate the psychological and social development
- Work that harms child's self-esteem as in bonded labor and prostitution.

EVOLUTION OF CHILD LABOR

Participation of children in work is prevalent in different forms in every society throughout human history. Since the earliest times, children have been involved in and contributed to the economic activities of their respective families. In many societies, a gradual incorporation of the child into the work activities occurs between the age of 5 years and 15 years. Children begin their work activities within their family through which they learn various skills from their guardians without any ill treatment and this type of work is practically free from harmful effects and can be educational and socially useful. In many societies, older children are compelled to work in order to pay for the education of the younger siblings. Older children are sometimes absorbed to assist the petty business of their parents and are not allowed to go out of the home premises.

With rapidly changing societal formation, children can be seen performing a number of jobs which, by their nature, are hazardous to their growth and psychological development. The important point here is that the growing phenomenon of child labor in urban areas is still a global concern and it will continue to be more acute in future. The growth rate of agricultural sector has relatively gone down which has given rise to the problems of both regional and sectorial disparities in development.

Today, the child workforce has to perform at par with adults, without parental guidance, and outside the environs of their families which involve a sharp change in environment, discipline and lifestyle. They work alone or along with other workers, and perform different types of repetitive, uninteresting and hazardous jobs and are often maltreated and exploited.

DEMOGRAPHIC PROFILE

The term *child labor* has been interpreted differently by different people. Child workers are a highly visible part of workforce in many countries. International Labour Organization (ILO) estimates the number of working children aged between 5 years and 14 years to be about 250 million in the developing countries, of whom at least 120 million are working full time. In India according to 2001 census there were 12.6 million working children aged 5–14 years. Main workers are those who are engaged in a full time economic activity and marginal workers are those who are part time workers.

FORMS OF CHILD LABOR

In India, no systematic and exhaustive documentation of the types and nature of work have been compiled. In general, children

are engaged in a number of activities—visible, invisible, formal, informal, paid or unpaid. Moreover, both in rural and urban areas child work vary between boys and girls. It was also found that young boys were engaged in relatively larger number of occupations than young girls. In the urban areas of India children are doing a large variety of jobs compared to rural areas. Many children work in their families as helpers in different household chores. The rural children are often involved in nondomestic work which is largely agricultural in nature and many of them are involved in work which is generally seasonal. Following are the types of work in which urban children are concentrated:

- *Within the family*
  - *Domestic tasks:* Cooking, childcare, fetching water, cleaning utensils, washing clothes, care of livestock, etc.
  - *Handicrafts and cottage industries:* Weaving, leatherwork, woodwork, etc.
- *Within the family but outside the home*
  - Domestic help
  - Construction work
  - Mining
  - Informal economy, i.e., laundry, recycling rubbish, etc.
- *Outside the family*
  - Employed by others
  - Bonded slaves
  - Apprentices
  - *Skilled trades:* Weaving or carpet making-embroidery, brassware works, gem polishing, etc.
  - Industries, mines, etc.
  - *Commercial:* Shops, restaurants, hotels.
  - Begging
  - Prostitution and pornography.

CAUSES OF CHILD LABOR

The real causes of child labor are rooted in inequality and poverty. This has become conventional wisdom, but what does it really mean? To begin with, parents have little choice but to send their children to work; parents depend on their children, economically.

The population growth rates in developing countries have remained more or less same whereas the mortality rates have declined remarkably. This has resulted in the survival of a large number of children and a proportion of them have been found to be higher among the poor. Thus, poor families are left with only young children as potential workers. Major reason for the prevalence of child labor in India is not far to seek. Poverty is the primary and main reason for the prevalence of child labor, because their income is essential for the survival of the family as well as the child. Thus, poverty of parents compels them to send their children to work at an early age to almost all sectors of the economy, organized or unorganized. Summarily, The Government of India has identified poverty, lack of awareness among parents for educating children, illiteracy, large size of the family, inadequate schooling facilities, loss of parents or bread earners of the family, unemployment and lack of land as the causes of child labor.

DIFFERENT SECTORS OF CHILD LABOR

Most children in almost all societies work in one way or another, though the types of work they do and the forms of their involvement varies. The major forms of child participation can be broadly classified into four major categories:

1. Children are employed in factories and industrial enterprises including cottage and home industries, enterprises like cigarettes, brick kilns, weaving or carpet making, glass or pottery, and metal working. Children in the developing countries are employed and work long hours with low wages. In certain industries, a system of bonded labor prevails and the children are separated from their families and become subject to abuse and exploitation.

2. Second category is the agricultural sector including coffee, tea and tobacco plantations as well as the farms from family plots to commercial farming.

3. In the third category, children are employed in the service sector in work as domestic servants, helping in shops and restaurants, street cleaning, washing cars and rag-picking.

4. The fourth and overlapping category is the *children on the street*—the product of migration into megacities. Such children live on the streets, many without family connections and may be found earning their livelihood on any of the previous three categories of employment.

CHILD WORK AND IMPAIRED EDUCATION, HEALTH AND NUTRITION

Unfortunately all the members of the society in the developing world do not get access to education. When the children have not been enrolled in the school either due to poverty, shortage of schools or unwillingness on the part of children, they are found idle at home or on the streets. Moreover, parents of the working children strongly consider sending their children to learn practical skills instead of keeping them idle at home for future work prospects. Thus, compulsory schooling will not help parents or children unless it helps to develop an important skill and provides a meaningful basis for the subsequent labor entry. Before joining the labor force, the children are virtually idle at home. However, majority of the dropouts have expressed their willingness to avail educational facilities if they could combine work and study together. Thus, the following points should be taken into consideration for access to education:

- Ensuring that there are teachers at schools situated in the area of his or her occupation.
- Motivating the guardians to send their children to school in order to decrease the dropout rates.
- Arranging proper care of the school building and watching whether proper actions for removing deficiencies are being taken or not.
- Asking the government to open more and more new schools and ensuring the availability of reading materials.
- Encouraging the association of guardians and teachers, ensuring that their meetings are held from time to time and playing an active role therein.
- Announcing various incentives for sending children to school.
- To sensitize the common people on the issue of child labor and drawing the attention of village panchayat towards school education.
- The attention of the child workers should be drawn to the need for compulsory education.

Due to industrial revolution along with technological advancement it is possible to provide health-care all over the world. But this has not reached all sectors of the society. The government of India is making continuous efforts to improve the health status particularly in children. The labor increases their nutritional requirements. Normal growth spurts during puberty and adolescents are adversely affected by the poor diet available to most of the child workforce.

DOMESTIC CHILD LABOR

Child domestics or domestic workers are defined as children under the age of 14 years who work in other people's households, doing domestic chores, caring for children and running errands among other tasks. In some industrialized countries and in some emerging economies, there has been a decline in child domestic work as more children attend school and aim for qualified employment. On the other hand, in societies where the opportunities for employment is limited, cheap labor, poverty widespread, the sense of social hierarchy strong, the number of domestic workers are increasing within household and a wide variety of domestic tasks need to be taken. In nonindustrialized societies the domestic work load can be extremely heavy. There is always a demand for young domestic workers, mainly the girls because they are cheaper to hire and more malleable and cost less. This is often the case of modern middle class households where both the parents go out to work. Thus, the phenomenon of child domestic workers is a complex situation that has evolved from unchallenged social practices and prevailing socioeconomic reality.

BONDED CHILD LABOR

Bonded labor is prevalent in some developing countries like India, where the peasant family is committed to providing certain labor services by custom often in return of repayments of debt. One form of bonded labor is where children are pledged to landlords, often as domestic servants as part of debt for all throughout their lives. In many of these situations, child workers are neglected and have poor nutrition and bad health. In India 8.7–21% bonded laborers are below 16 years of age. Another rapidly emerging form of child labor is contractual or nonformal work under private armies and militia. Here, the children have been frequently deployed as soldiers or paramilitary personnel. There may be some benefits in the form of regular food, clothing, shelter, and medical attention to these children but these can hardly compensate for the danger of exposure to extremely hazardous work.

IN A NUTSHELL

1. Child labor exploits children in terms of long hours of work, hazardous working condition, and lack of health-care, schooling and recreational facilities which ultimately threaten the health and overall development of children.
2. Child labor is a global menace. In developing countries, about 250 million children 5–14 years of age are engaged in child labor. Corresponding figure for India is 12.6 million (2001 Census).
3. Children are engaged in work everywhere: homes, factories, shops, farms, streets, etc. Begging, prostitution, warring, bonded slavery are the worst forms of child labor.
4. The Government of India has identified poverty, lack of awareness among parents for educating children, illiteracy, large size of the family, inadequate schooling facilities, loss of parents or bread earners of the family, unemployment and lack of land as the causes of child labor.
5. Child labor continues despite legislation to ban it; the solution lies in alleviating poverty and creating unconditional opportunities for fulfilling the basic requirement of all children: food, shelter, protection, and education.

MORE ON THIS TOPIC

Banerjee SR, Bharati P, Vasulu TS, et al. Whole time domestic child labor in metropolitan city of Kolkata. Indian Pediatr. 2008;45:579-82.

Banerjee SR. Child Labor. Indian Pediatr. 1990;27:3-6.

Banerjee SR. Female working children. Indian Pediatr. 1990;27:1153-5.

Dalal K, Rahman F, Jansson B. The origin of violent behaviour among child labourers in India. Glob Public Health. 2008;3:77-92.

Kabir Z. Child labour and urban slum experience. Indian J Pediatr. 2003;70:447.

Kuriakose JR. Child labour--the ill effects on health. Nurs J India. 2012;103:79-81.

Mishra D, Arora P. Domestic child labor. Indian Pediatr. 2007;44:291-3.

Mondal R, Sarkar S, Bhattacharya S, et al. Profile of child labor in Indian railways. Indian J Pediatr. 2012;79:1347-50.

Venkateswarlu D, Kasper J, Mathews R, et al. Child labor in India: a health and human rights perspective. Lancet. 2003;362 Suppl:s32-3.

Chapter 50.4
Child Abuse and Neglect
Kiran Aggarwal

Child abuse is more than just bruises or broken bones. Ignoring children's needs, putting them in unsupervised, dangerous situations, or making a child feel worthless or stupid is also considered as child abuse. It has serious physical and psychosocial consequences, which adversely affect the health and overall well-being of a child. Child abuse in society has been endemic for generations; a very small percentage is visible, like the tip of the iceberg. Unlike acute and chronic illnesses, despite causing so much harm to the child and impacting them in adolescence and in adulthood, it is not reported.

Why do Pediatricians Need to Address the Problem of Child Abuse?
Sensitization of medical professionals about their obligation towards children and society is a crucial aspect of attitudinal learning. Pediatricians are often the first contact of a child who has suffered abuse. In the outpatient department or casualty, whenever one comes across a case of child abuse, chances are that the severity may often determine whether we do suspect it or fail to recognize the subtle varieties. The pediatrician can only recognize all such cases, when he or she considers every child seen by him or her to be potentially at risk of either abuse or neglect.

What is Expected from Pediatricians while Encountering a Child with Suspected Abuse?
Pediatricians should be able to recognize abuse and neglect and treat consequences of it. They should be able to build expertise in presenting medical evidence while dealing with a case of child abuse in a multidisciplinary approach **(Box 1)**. The primary focus of any interview with a child should be the child's needs and comfort level. Pediatricians should know law of the land. In view of the mandatory reporting of sexual abuse under *Protection of Children against Sexual Offences (POCSO) Act, 2012,* they should know the consequences of not reporting such offences. Their duty is to report and not investigate; be polite and respectful to the family throughout; and preventing further abuse to the child. While working in the best interests of the child, removing children from the caregivers should be the last resort.

HISTORY OF CHILD ABUSE
Until the 18th Century, children were viewed by the society as possessions of their parents who were at liberty to treat children in any way they wished to. In fact legislation was introduced to protect animals before children were afforded the same *privilege*. Lynch (1985) examined evidence produced throughout the centuries on the recognition of physical abuse, and found that those caring for children might actually injure them.

The 20th Century saw the beginnings of an acknowledgment of the problem of child abuse and recognition that children needed protection. Society was slow to accept that carers could deliberately harm children for whom they were responsible. In 1946, Caffey, a pediatric radiologist in USA, described bone lesions and subdural hematomas resulting from trauma, and Kempe, in 1962, described the *battered child syndrome*. The term *nonaccidental injury* became the medically accepted label for this syndrome in UK, and doctors became increasingly involved with social workers and the police in its diagnosis.

In 1966, the British Pediatric Association (BPA) published a position paper on the battered baby syndrome. Physical abuse of children was established to be a common occurrence and the beginning of its management by the medical, social work and police professionals began in the 1970s. It was only in the mid-1980s that the problem of child sexual abuse (CSA) was seriously highlighted; defining what constitutes child abuse remained a matter of debate. Since 1982, the term Munchausen syndrome by proxy (MSBP) has been used where a caregiver (usually the mother) complained of nonexistent symptoms in the child, often causing harm in the process.

DEFINITIONS
The *United Nations Convention on the Rights of the Child (UNCRC)* 1989, defined a child as every human being below the age of 18 years unless, under the law applicable to the child, majority is attained earlier. After the introduction of the Juvenile Justice (Care and Protection) Act, 2000 (amended 2006/2011), for all practical purposes, a child is considered as a person below 18 years, but most of the Government programs on children in India are still targeted for the age group below 14 years.

According to WHO, child abuse constitutes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity, in the context of a relationship of responsibility, trust or power.

- *Physical abuse* of a child results in actual or potential physical harm from an interaction or lack of interaction, which is reasonably within the control of a parent or person in a position of responsibility, power, or trust. There may be single or repeated incidents.
- *Child sexual abuse* is the involvement of a child in sexual activity that she or he does not fully comprehend, is unable to give informed consent to, or for which the child is not developmentally prepared, or that violates the laws or taboos of society. CSA is evidenced by an activity between a child and an adult or another child who by age or development is in a relationship of responsibility, trust or power; the activity being intended to gratify or satisfy the needs of other person. This may include but is not limited to: the inducement or coercion of a child to engage in any unlawful sexual activity; the exploitative use of a child in prostitution or other unlawful sexual practices; and, the exploitative use of children in pornographic performances and materials.
- *Emotional abuse* includes the failure to provide a developmentally appropriate, supportive environment, including the availability of a primary attachment figure, so that the

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BOX 1 Views of President of Royal College of Pediatrics and Child Health, 2006

"Child protection is an important part of every doctor's business. It is a core activity for pediatricians and one which, if we get it right, can make a real difference to the health and well-being of a child. If we get it wrong, it can cause untold misery for the child, the family and professionals involved.

Child protection is not something that should be a burden to pediatricians. It should be a satisfying area of clinical practice with a good and measurable outcome for the child, either restored to his/her own family or in alternative care arrangements. There can be few greater achievements then to see a child restored to an environment where they can grow and developed in safety."

child can develop a stable and full range of emotional and social competencies commensurate with his or her personal potential, and in the context of the society in which the child dwells. There may also be acts toward the child that cause or have a high probability of causing harm to the child's health or physical, mental, spiritual, moral or social development. These acts must be reasonably within the control of the parent or person in a relationship of responsibility, trust or power.

- *Neglect* is the inattention or omission on the part of the caregiver to provide for the development of the child in all spheres: health, education, emotional development, nutrition, shelter and safe-living conditions, in the context of resources reasonably available to the family or caretakers and causes, or has a high probability of causing harm to the child's health or physical, mental, spiritual, moral or social development. This includes the failure to properly supervise and protect children from harm as much as is feasible.

INCIDENCE AND PREVALENCE

It is estimated that about 40 million children between 0 year and 14 years of age suffer from abuse or neglect and require health or social care. Statistics reveal that child abuse, in all its forms, physical, sexual, emotional and neglect, is common in India, across all strata of society. The UN Secretary General's Study on violence against children has given the following overview of the situation of abuse and violence against children across the globe:

- WHO estimates that almost 53,000 child deaths in 2002 were due to child homicide.
- An estimated 150 million girls and 73 million boys under 18 have experienced forced sexual intercourse or other forms of sexual violence involving physical contact.
- UNICEF estimates that in sub-Saharan Africa, Egypt and Sudan, 3 million girls and women are subjected to female genital mutilation (FGM) every year.
- International Labor Organization (ILO) estimates that 218 million children were involved in child labor in 2004, of whom 126 million were engaged in hazardous work. Estimates from 2000 suggest that 5.7 million were in forced or bonded labor; 1.8 million in prostitution and pornography and 1.2 million were victims of trafficking.
- Only 2.4% of the world's children are legally protected from corporal punishment in all settings.

Child Abuse in Asia

While certain child abuse and neglect issues are common in almost all countries but many issues which are prevalent only in certain regions of the world. In Asia, where population density is high, the issues of child labor and child sexual exploitation are also high. Political instability and other internal disturbances, including conditions of insurgency are also creating major problems, with increasing number of child soldiers, refugee children, trafficked children and children on the streets.

Natural and man-made disasters kill, injure, or displace large number of children in developing countries. Direct risks for children in natural disasters include deaths, injuries, vulnerability to malnutrition and infectious diseases, loss of routine activities, acute post-traumatic stress disorder and long-term psychological trauma and all types of abuse, neglect and exploitation.

The use of so-called lower castes and downtrodden women and children for prostitution in South Asia has been legitimized by society through religious justification. *Balkey* and *Ashnas* in Pakistan (Khan 2000), *Devdasi* in India, *Deuki* in Nepal, all bear testimony to this persecution of women and children in the garb of religion. Gender discrimination in some developing countries subject the girl child to unacceptable persecution, ranging from infanticide, feticide to child marriage and malnourishment.

Child Abuse in India

India is home to the largest number of children in the world. 19% of the world's children live in India. There are about 43 crore children in the age group of 0–18 years. This is an enormous number of children that the country has to take care of. It is estimated that about 40% of Indian children are in difficult circumstances (Report MWCD–Child Abuse Study, 2007).

ETIOLOGY

Factors Contributing to Child Abuse and Neglect

Several theories have been proposed, but no single theory or known cause stands alone nor is there any single description that captures all families in which children are victims of abuse and neglect. Research has recognized a number of risk factors, which are listed in **Box 2**.

HOW TO SUSPECT CHILD ABUSE AND NEGLECT

According to the level of concern, one has to either *consider* or *suspect* abuse. To consider child abuse means abuse is one possible explanation for the alerting feature or is included in the differential diagnosis. To suspect child abuse means a serious level of concern about the possibility of child abuse but is not proof of it. An unsuitable explanation for an injury or presentation is one that is not probable or inadequate. If a health-care professional comes across an alarming sign or symptom of possible child abuse suggesting to consider, suspect or ruling out child abuse as a possible explanation, it is good practice to follow the systematic process.

BOX 2 Factors contributing to child abuse and neglect

1. Parent or caregiver factors
   a. Parent's abusive childhood and the cycle of abuse
   b. Unrealistic expectations from children
   c. Lack of support
   d. Alcohol and drug abuse
   e. Personality characteristics and psychological well-being of parents
2. Family factors
   a. Specific life situations of some families promoting conflict
   b. Family structure involving broken families or abusive families
   c. Marital conflict and domestic violence
   d. Stress
   e. Parent-child interaction with negative reinforcement
3. Child factors
   a. Younger children
   b. Children with disabilities
   c. Other child characteristics
   d. Aggression, attention deficits, difficult temperaments, and behavior problems—or the parental perceptions of such problems
   e. Doubts of paternity
   f. Girl child
4. Environmental factors
   a. Poverty
   b. Unemployment
   c. Social isolation
   d. Poor living standards and socioeconomic inequalities
   e. Existence of child labor, child prostitution, child pornography
   f. Social norms promoting or glorifying violence towards others
   g. Social acceptability for corporal punishment
   h. Transient neighborhoods, e.g., migrant labor
   i. Easy availability of alcohol and drugs
5. Protective factors
   a. Supportive, emotionally satisfying relationships
   b. Network of relatives or friends
   c. Programs on marriage education, birth of the first child, parenting adolescents, and gender discrimination.

1. Listen and observe
2. Demand an explanation
3. Document
4. Consider, suspect or rule out abuse
   (a) Consider:
      - Discuss your concerns with a more experienced colleague.
      - Try collecting collateral information from other agencies and health disciplines, for an overall assessment of the child.
      - Review at a later date, looking out for recurrence of similar occurrence of this or any other alerting features.
   (b) Suspect:
      - Refer to children's social care (child welfare committee)
      - Trigger a child protection investigation
      - Offer supportive services to the family following an assessment or alternative explanations may be identified.
   (c) Rule out:
      - Suitable explanation is found for alerting features.
5. *Record* Record all actions taken in step 4 and the outcome.

DIAGNOSTIC CONSIDERATIONS

An injury was inflicted by a caregiver or caused by accidental means is more than a medical determination, and a matter of serious concern of the current and future safety and well-being of the child and the family. In all injuries, the major differential diagnosis is between accidental and nonaccidental injury. Determination of accidental or nonaccidental injury is best accomplished through medical evaluation with information gathered through a multidisciplinary investigation, at times involving child protective services and law enforcement agencies **(Box 3)**.

Bruises

Bruises are the most commonly found manifestation in an abused child. Conditions simulating bruising include Mongolian spots, birth marks, blood dyscrasias, hemophilia, Ehlers-Danlos syndrome, and Henoch-Schönlein purpura. Noninflicted bruises are usually on bony prominences. Presence of underlying medical condition does not rule out abuse. In a clinical examination, color or any other marker cannot reliably judge age of the bruise.

Burns

Burns caused by momentary lapse in supervising the child should not be blamed as parent's neglect in absence of other signs of abuse. Conditions simulating burns include hemangioma, and impetigo can simulate cigarette burn.

Fractures

Inflicted fractures are more common in children younger than 18 months. No fracture characteristic is specific for abuse in isolation. Fractures in children due to inflicted injury can be divided into three categories:
1. *Highly specific* Injuries include classic metaphyseal lesions, rib fractures, scapular fractures, spinous process fractures, and sternal fractures.
2. *Moderate specificity* Fractures include multiple fractures (especially if bilateral), fractures of different ages, epiphyseal separations, vertebral body fractures, digital fractures, and complex skull fractures.
3. *Low specificity* Fractures include clavicle fractures, long bone shaft fractures, and linear skull fractures.

Moderate and low specificity fractures are more concerning without a credible history of accidental trauma, particularly in

BOX 3 History of the circumstances surrounding the child abuse

Whenever a child is injured, a complete history of the circumstances surrounding the injury, as well as a detailed injury history, is essential. Basic questions may be asked as:
- When was the child last perfectly well?
- What was the date and time of the injury and when was it first noted?
- Where did the injury occur?
- Who witnessed the injury?
- What was happening prior to the injury?
- What did the child do after the injury?
- What did the caregiver do after the injury?
- How long after the injury did the caregiver wait until seeking care for the child?
- What symptoms were the child exhibiting, and what, if any, remedies did the caregiver attempt?
- Inquire about specific details related to the injury, such as height of the fall, landing surface, and temperature of water (if scald burn), among others.
- The past medical history should be explored for general health and previous trauma and hospitalizations, as well as for the source of health-care and developmental and social aspects of the child's life. In cases of maltreatment, the history is often inaccurate and misleading. The following historical elements should raise concerns for possible physical abuse:
  - Details are inconsistent among caregivers.
  - Caregivers give implausible details not correlating with the trauma observed on examination.
  - Caregivers describe minor trauma, but the child displays major injury on examination.
  - No history of trauma is offered at times.
  - Injury described as self-inflicted is not possible given the age/developmental abilities of the child.
  - Caregivers demonstrate a significant delay in seeking treatment for the child.
  - Serious injury is blamed on a younger sibling/playmate.
  - Caregiver frequently changes health-care facilities, pediatricians, or emergency departments.

infants. Fractures in children older than 2 years is likely to be non-inflicted unless multiple and in absence of other signs of abuse. Conditions simulating fractures include: Osteopenia, osteogenesis imperfecta, metabolic and nutritional disorders (scurvy, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, and neoplasia. Family history of recurrent fractures after trauma should be obtained.

Shaken Baby Syndrome

Abusive head trauma (AHT), previously known as shaken baby syndrome, is a clinical syndrome caused by violent shaking of young infants, often followed by an impact to the head from being thrown or slammed onto a fixed surface. These actions may cause retinal hemorrhages and intracranial trauma of varying severity.

Visible head trauma or neurological symptoms may not be there always, which does not exclude the need for neuroimaging. The examination should include head circumference, palpation of the anterior fontanel, neurological examination, and a thorough skin examination. Compared with severe accidents, inflicted head trauma is more likely to have: subdural and subarachnoid hematomas; multiple subdural hematomas of differing ages; extensive retinal hemorrhages; and associated cutaneous, skeletal, and visceral injuries.

Other Injuries

Oral injury is common in both accidental and nonaccidental injury. It is differentiated by history and the developmental capabilities of the child. Inflicted oral injuries include torn labial or lingual

frenula, contusions, burns, and fractured, displaced, or avulsed teeth or facial bones. Inflicted abdominal trauma often does not have physical findings, but abdominal distention, tenderness to palpation, bruises, low systolic blood pressure, femur fracture warrant further evaluation.

Munchausen Syndrome by Proxy

In this condition, caregivers either grossly exaggerate a trivial illness (e.g., a urinary tract infection may be exaggerated as renal failure), totally fabricate symptoms (e.g., epilepsy) or may even induce signs in a variety of ways (laxative to cause diarrhea, salt causing renal failure, suffocation to induce cyanosis and apnea, tampering the biological samples for investigations or even tampering with the vital treatment). This has also been called *Perplexing Presentations* in a Royal College of Pediatrics & Child Health Guidance (RCPCH, 2013). The prevalence is quoted to be 0.5 per 100,000 in children under 16 but 2.8 per 100,000 in under 1 year age. This is based on ascertained cases of nonaccidental suffocation and nonaccidental poisoning reported between 1992 and 1994 in the UK and the Republic of Ireland (McClure, 1996).

In *fabricated* or *induced* illness, the caregivers harm children. This uniquely presents as an illness or a neurodevelopmental disorder (epilepsy, high functioning autism, etc.) hence a general medical practitioner or a pediatrician would be involved, who if not aware, may unwittingly become an adversary.

Etiology

Why some caregivers resort to such actions can vary widely. Some may do it for a gain, others may be overanxious and para-doxically over protective, others may have mental health problem (depression, psychosis, obsessive-compulsive disorder, etc.) and few indulge in such actions relentlessly and in a pervasive manner with no apparent gain. The last one qualitatively denotes a phenomenon called Munchausen syndrome by proxy or MSBP (Meadow, 1982).

Diagnosis

Diagnosis should be suspected in the following situations:
- In a child who has multiple medical problems not responding to treatment or that follow a persistent and mysterious course.
- If physical or laboratory findings are highly unusual, not correlating with the medical history, or physically or clinically impossible.
- Where short-term symptoms may improve or stop when the victim is not with the perpetrator (for example, when hospitalized).
- If the parent or caregiver is not happy with the test results as normal but continues to believe that the child is ill and may initiate "doctor shopping" to find a professional who believes at last.
- If the parent or caregiver appears to be medically knowledge-able and fascinated with medical details or seems comfortable in the hospital environment and attention the sick child receives.
- If the parent or caregiver is extrasupportive and encouraging to the treating doctor, or is angry and demands further intervention, more procedures, second opinions, or referrals to more sophisticated health facilities.
- Parent or caregiver may confess.

Management

Management includes treatment of both victim and the family.

It consists of a multiagency or multidisciplinary approach. To start with if a general medical practitioner suspects this condition then a referral to a pediatrician and sharing of suspicion will be needed without first alerting the suspected perpetrator. Pediatrician should evaluate the clinical situation objectively and pursue any further investigation only if necessary.

If a pediatrician suspects this condition a discussion with other colleagues and someone with more experience in this area would be necessary without first sharing the suspicion with the suspected perpetrator. In MSBP, risk to the child increases at the point of disclosure of the suspicion to the perpetrator. There is also high probability that the child may then be withdrawn from the current medical follow-up only to reappear somewhere else afresh.

Once there is a consensus about harm occurring to the child, a multiagency discussion should take place. If the perpetrator is assessed to be overanxious and doing it unwittingly then they need to be reassured the best way possible involving the whole family. If there is adverse family dynamics (e.g., domestic abuse where the perpetrator is a victim) then disclosing to the spouse or other family members can be risky and the situation should be expertly assessed. If a mental health problem is suspected, an appropriate referral to a psychologist or a psychiatrist needs to be made with support from the family.

If the true MSBP is suspected, involvement of the police and other statutory agencies should be seriously considered from the outset to gather evidence in a way that could be admissible in the court. Generally, risk of death is greater in infants and younger children if the presentation is of more serious nature, e.g., nonaccidental suffocation, nonaccidental poisoning, nonaccidental near drowning, etc. Ideally there should be a clear protocol for action in all hospitals and practices drawn up by a multiagency group.

CHILD SEXUAL ABUSE

Childhood sexual abuse (CSA) is a complex life experience, not a diagnosis or a disorder. An array of sexual activities is covered by the term CSA. This diversity in itself ensures that there will be a range of outcomes. Interestingly, boys are abused equally as girls but may not have the protective shield of the family structure and recognition, as girls do.

Etiology

Why people sexually abuse children has been one of the foremost questions guiding research on sexually deviant behavior in the 20th century. There are various explanations as to the etiology and maintenance of sexual offending. Due to the heterogeneity of the perpetrators of such abuse and the complex nature of this behavior, no one theory adequately explains: (a) the motivating factors that lead an adult to have sexual relations with a child and (b) the sustaining factors that contribute to the continuance of such relations (Bickley & Beech, 2001).

Types of Child Molesters
- *Fixated or preferential*, child molesters are exclusively attracted to children. They are likely to have many victims as a result of their failure to develop sexual attraction to their age mates. Also called pedophiles.
- *Regressed offender* in contrast is sexually attracted to age mates, but some type of stressor in the environment triggers the abuse. Regressed offenders display greater guilt and shame and exhibit a positive treatment prognosis, it is possible to teach them to identify their high-risk situations.

Pattern of Events

The delay between the initial happening and the subsequent disclosure of the abuse varies, depending on a number of factors such as the age and the gender, relationship with the perpetrator, severity of the abuse, developmental and cognitive variables,

and likely consequences of the disclosure. Consequently, CSA is significantly underreported. When victims do report, they often do so years after the abuse occurred making the subject all the more difficult to deal with.

The "child sexual abuse accommodation syndrome", propounded by Summit (1983), proposes that children's responses to CSA comprise of five stages: secrecy; helplessness; entrapment and accommodation; delayed and unconvincing disclosure; and recantation.

The typical pattern of events is as follows: the child is forced to keep the sexual abuse a secret and initially feels trapped and helpless. These feelings of helplessness and the child's fear that no one will believe the disclosure of abuse leading to accommodative behavior. If the child does disclose, failure of family and professionals to protect and support the child adequately, augment the child's distress and may lead to retraction of disclosure.

Presentations of Child Sexual Abuse

- *Child exhibiting sexually explicit behavior:* Sexual behavior inappropriate to age or developmental capabilities. Adolescents may become sexually promiscuous or sexually abusing younger children.
- Disclosure to a trusted adult
- *Behavior change:* Social withdrawal, fearfulness, distractibility, learning difficulty, lack of concentration due to stress.
- Regression in developmental milestones
- Depression
- Secondary enuresis/encopresis
- Experimenting with drugs/alcohol
- Running away from home
- Watching sexually explicit photographs/videos
- Pregnancy
- Some of the children will never explicit abnormal behavior during childhood but can have adverse effects in late adolescent or adult life.

When to Suspect?

Medical History

Most important evidence in CSA is *verbal evidence*: exactly what child has to say **(Box 4)**. Medical history should be nonleading, nonsuggestive, nonjudgmental, empathetic, ideally should be done independently without any caregiver around. Children may be hesitant to talk in their presence simply for the reason they would not like them to get upset.

If skillfully taken medical history can be very different than they are supposed to share with the child protection services (CPS) or law enforcement as the children carry very special relationship with their doctor if the fear of needles and pricks are removed from their minds. There is a relationship of confidence and trust that the doctor will help them.

Suspect sexual abuse if a girl or boy has:

- A genital, anal or perianal injury (as evidenced by bruising, laceration, swelling or abrasion) and the explanation is absent or unsuitable.
- A persistent or recurrent genital or anal symptom (for example, bleeding or discharge) associated with behavioral or emotional change that has no medical explanation.
- An anal fissure, and constipation; if Crohn disease and passing hard stools have been excluded as the cause.

Consider sexual abuse if:

- A gaping anus in a girl or boy is observed during an examination and there is no medical explanation (for example, a neurological disorder or severe constipation).

BOX 4 Preparing a child for medical history

- Introduce yourself; tell what you do?
- Let the child know there will be no pricks or needles.
- Let the child know you talk to children who are worried about similar issues.
- Most do not tell about these things: why did you decide to tell?
- Who do you think is responsible for what had happened?
  - If child thinks it is his/her fault issue should be addressed
- Do you have any worries about your body because of what happened or you had to do?
  - Some children do express such worries: need to address issues
- To understand child's experience its necessary to address some issues
  - Circumstances and reasons surrounding disclosure
  - How the perpetrator approached the child
  - Details of the first sexual encounter and further progression of sexual advances over the time
  - Worries regarding body image
  - Questions clarifying child's perception of the interaction in regard to penetration
  - Exposure to pornography or on being photographed
  - Recantation
- Some specific complaints related to genitourinary or gastrointestinal signs and symptoms associated with the sexual contact.
- Any threats or statements made by perpetrator to the child to keep secrecy.

- A girl or boy has a genital or anal symptom (for example, bleeding or discharge) without a medical explanation.
- A girl or boy has dysuria (discomfort on passing urine) or anogenital discomfort that is constant or recurrent and does not have a medical explanation (e.g., worms, urinary infection, skin conditions, poor hygiene or known allergies).
- Evidence of one or more foreign bodies in the vagina or anus. Foreign bodies in the vagina may be indicated by offensive vaginal discharge.
- Sexually transmitted infections.

Decision to Report

All health-care professionals including pediatricians should know about mandatory reporting if encountered suspected CSA case under POCSO Act, 2012. Lapses in reporting are punishable in form of imprisonment and fined.

Physical Examination where Sexual Abuse is Suspected

Only 5% of children undergoing medical evaluation following sexual abuse are generally found with abnormal findings. Abusive acts in children, e.g., digital penetration and fondling, etc., may not cause trauma. Disclosure may be quite delayed in children and genital trauma may heal by that time. All these can explain to some extent why only 5% of all evaluations are with abnormal findings.

Ministry of Health and Family Welfare, Government of India has come out with detailed *Guidelines and Protocols on Medicolegal Care for Survivors/Victims of Sexual Abuse* management of sexual abuse in February, 2014. Pediatricians can play a major role to address CSA in detecting, reporting, investigating and treating sexually transmitted infections, supporting and assuring children and families, prevention of CSA by educating children and their caregivers about good touch and bad touch and how to keep them safe. Pediatricians can do triage and refer to expert. In case of suspicion reporting can be done at any stage.

POCSO Act, 2012 makes everyone working with children to work or act in the best interest of the child in a child-friendly way with several other provisions to safeguard the interest of the child in all respect.

Assessment and Management of Possible Sexual Abuse

- *Genital findings simulating sexual abuse can be*: Infections caused by *Neisseria*, yeast, nonspecific vulvovaginitis, group A *Streptococcus*, *Haemophilus*, eczema, rarely lichen sclerosis.
- *Vaginal discharge*: It can be caused by foreign body, sexually transmitted infections, infection by organisms, e.g., *Salmonella*, *Shigella*, *Yersinia*, or simply can be there due to onset of puberty.
- *Genital ulcers*: They can also be caused by Syphilis, Herpes simplex virus, Epstein-Bar virus, Varicella-Zoster, Crohn's disease, Behçet's disease.
- *Vaginal bleeding*: Can be caused by accidental injury, foreign body, urethral prolapse or any tumor in vagina.
- *After ruling out other medical conditions*:
  - Sexual abuse is a manmade disaster for a child and the principles applied in management of disaster should apply considering it as medical emergency in acute situations.
  - Triage process for any suspected sexual abuse should be initiated.
  - It is crucial to know the timing of the occurrence and child is prepubertal or postpubertal?

In Prepubertal Child

- *Within 72 hours*
  - Forensic evidence collection (external genitalia, vaginal and oral swab) should be done and child should be referred to a health facility equipped to collect the forensic evidence.
  - If victim's condition demands life saving measures any nearest health facility equipped to deal with the emergencies should be used without wasting crucial time.
- *If incident occurred more than 72 hours back*

  - In prepubertal child evidence from forensic material collection remains very low and may not be necessary.

For Postpubertal Children

- Evidence from forensic material collection can be obtained even up to 120 hours.
- If child does not present with acute emergency, examination can possibly be postponed till the next morning, which can be even an outdoor clinic setting where child can be even interviewed in a bit relaxed state of mind.
- In another situation child can give disclosure at pediatrician's clinic where opportunity can be had to interact with the child in developmentally appropriate way separately from the caregiver.
- Parents can be calmly told talking separately to the child is part of the process of assessment.
- Talking to the child should start with rapport building with some general conversation empathetically with self-introduction with open ended questions avoiding leading questions.
- Very young children or developmentally delayed children may not be that verbal and in that case caregiver's information will have to be believed without interviewing the child.
- Reporting does not need certainty of sexual abuse happening. Even just the inappropriate sexual behavior can be reported even if child not giving any verbal clue.

Table 1 summarizes the various samples, site and technique of sample collection in suspected sexual abuse.

GENERAL PRINCIPLES OF PREVENTION

Primary (universal) prevention Information, education, support to all children to help protect them from being abused or from

Table 1 Sample collection in suspected sexual abuse

Site	Material	Equipment	Technique
Clothing	Clothes	Paper bags	Patient is asked to stand on a white sheet of paper and undress herself. Clothes are put in separate paper bag.
Debris collection	Dust, fiber, etc.	Forceps	Pick any debris from the body or clothes and put in an envelope.
Finger nail Clipping or scrapings	Skin, blood, fibers, etc.	Toothpick Nail clipper Cotton swab	Toothpick is used to collect material from under the nails. Nails can also be clipped and placed in a sterile container. A swab can be collected.
Hair Pubic hair combings Pubic hair clippings Matted pubic hair	Hair and semen	Comb and scissors	Pick any debris and put it in a envelop Place a paper under the buttocks of the patient, comb the pubic hair and collect loose hair in the same paper and seal in the envelope. Matted pubic hair can be clipped with scissors and separately sealed in an envelope.
Vaginal swabs	Semen, sexually transmitted organism	Sterile cotton swabs and tube	Collect the swabs from the posterior fornix. Prepare the slide from the swab and place the swab separately in a tube
Endocervical swabs	Semen, sexually transmitted organism	Sterile cotton swabs and tube	Fluid and mucus is collected from the cervix and slide prepared. The swab is placed in the tube and sealed. Another swab is taken and stroked on a chocolate agar plate and swab discarded.
Washing from the vagina	Semen	Saline, syringe	Saline wash of the vagina is done by a preloaded syringe; fluid is withdrawn, smeared on a slide and examined there and then for spermatozoa under a microscope.
Perianal, anal, rectal swabs	Semen	Cotton swabs (dry or moist) and slides	Cotton swabs are used to collect the material.
Blood		Tube	Blood is collected for DNA profile, toxicology screen, blood grouping, HIV, hepatitis B and C and syphilis.
Urine		Appropriate container	Urine is collected for alcohol, toxicology screen and pregnancy testing.

Source: Puri M, Madan M. Sexual assault: care of a victim. AOGD Bulletin. 2013; Vol 12:13-16. Based on DHR Forensic Medical Care for Victims of Sexual Assault-Available from www.icmr.nic.in/dtr/pdf/1%20DHR%20Forensic%20Medical%20Manual%20Sexual%20Assault.pdf

offending, now or later in life, e.g., supporting in developing strong attachments, relationships, good sense of boundaries, respect, etc.

Secondary prevention Focuses on *at risk* people, groups and places, e.g., work with families with complex structures, isolated children with low self-esteem, families where there is a lack of boundaries or privacy or those individuals who already recognize they have concerning sexual thoughts about children.

Tertiary prevention Preventing revictimization; preventing recidivism. Applies to those already affected by CSA. Priority target groups include detection and counseling of abusers or potential abusers, adults who have sexually abused children or recognize that they have sexual thoughts or feelings towards children; and children and young people with sexually harmful behavior. Survivors of sexual abuse, adult survivors of childhood sexual abuse, and children and young people with residual disabilities need emotional support and rehabilitation.

Prevention of CSA Dealing with Sexual Misbehaviors

Most sexual misbehavior is common and normal. If adults respond to these behaviors appropriately, children will learn appropriate behaviors. Unfortunately, common sexual misbehavior is responded in such a way that may accelerate normal behavior into abuse of other children. There is need to respond to children with sexual misbehavior issues appropriately for healthy sexual development.

Prevention of CSA: Working with Boys

- Protection from victimization
- Indian boys and the sociocultural factors that work against them. Protective shield should be provided to boys equally as to the girls.
- Preventing the development of sex offenders.

Pediatricians can Teach Parents

- To minimize opportunity for perpetrators to access children by limiting one child or one adult situation.
- For being sensitive to any adult's unusual interest in young children.
- Helping parents to teach how to talk to children about what to do if confronted with abusive situation.
- Teach children to say *No*, *To leave* the parent or any other adult.
- Tell parents about signs and symptoms in child if encountered abuse.
- Tell parents how to talk without hesitating to their children to communicate without discomfort.

MORE ON THIS TOPIC

Aggarwal K, Dalwai S, Mishra D, Galagali P, Thandani A, Prasad C, et al. Recommendations on recognition and response to child abuse and neglect in the Indian setting. Indian Pediatr. 2010;47:493-504.

Banwari GH. Adolescent male peer sexual abuse: an issue often neglected. Indian J Psychol Med. 2013;35:394-6.

Behere PB, Mulmule AN. Sexual Abuse in 8-year-old Child: Where Do We Stand Legally? Indian J Psychol Med. 2013;35:203-5.

Dhawan J, Gupta S, Kumar B. Sexually transmitted diseases in children in India. Indian J Dermatol Venereol Leprol. 2010;76:489-93.

Guidelines & Protocols on Medicolegal Care for Survivors/Victims of Sexual Abuse. New Delhi: Ministry of Health and Family Welfare, Government of India; 2014.

Harendra de Silva DG, Hobbs CJ. Managing Child Abuse: A Handbook of Pediatrics for Medical Officers. New Delhi: WHO Regional office for South East Asia; 2004.

Karthiga RK, Ravikumar R. Child sexual abuse in Madurai, India: a literary review and empirical study. J Child Sex Abus. 2014;23:727-44.

Kiran K. Child abuse and neglect. J Indian Soc Pedod Prev Dent. 2011;29 (6 Suppl 2):S79-82.

Ministry of Women and Child Development. National Study on Child Abuse. New Delhi; 2007.

POCSO Act Rules; 2013.

Singhi P, Saini AG, Malhi P. Child maltreatment in India. Paediatr Int Child Health. 2013;33:292-300.

Working Group Report on women and children in the Eleventh Plan (2007-2012). Status of Indian Children. New Delhi: Ministry of Women and Child Development; 2007.

IN A NUTSHELL

1. Child abuse constitutes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity.

2. Factors contributing to child abuse and neglect include those related to the parents, family, child, and the environment.

3. If a health-care professional comes across an alarming sign or symptom of possible child abuse, it is good practice to follow the systematic process of listening, observing, demanding explanation, document, consider, and suspect or rule out abuse.

4. Abusive head trauma (AHT), previously known as shaken baby syndrome, is a clinical syndrome caused by violent shaking of young infants, often followed by an impact to the head from being thrown or slammed onto a fixed surface. These actions may cause retinal hemorrhages and intracranial trauma of varying severity.

5. Munchausen syndrome by proxy refers to the caregivers either grossly exaggerating a trivial illness, fabricate symptoms, or induce signs in a variety of ways.

6. All pediatricians should know about mandatory reporting if encountered suspected sexual abuse in children under POCSO (Protection of Children against Sexual Offences) Act, 2012. Lapses in reporting are punishable in form of imprisonment and fined.

Chapter 50.5
Adoption: Medical and Legal Issues
Samir H Dalwai

"The Goddess got into bed and clasping the burly hero to her bosom, pushed him through her robes and let him fall to the ground in imitation of real birth."—Diodorus Siculus describing Hera's adoption of Hercules, as quoted in James Frazer's *Golden Bough.* Primitive tribes continue this practice to this day.

INTRODUCTION

Adoption is an act of establishing a person as a parent to one who is not in fact or in law his child. Thus, adoption signifies the means by which a status of a legal relationship of parent and child between persons who are not so related by nature is established or created. As a result of a decree of adoption, the child, to all intents and purposes, becomes a child of the adoptive parent.

Adoption is an almost worldwide institution with historical roots traceable into mythology. The Egyptians and Hebrews knew of adoption and chronicled a famous example when the daughter of the Pharaoh adopted a son and called him Moses. The concept of *bringing up someone else's child as one's own* finds an echo in the story of *Karna* of *Mahabharata,* as also in the accounts of *Shakuntala* being brought up by *Rishi Kanva* and his wife. The object of adoption was also to secure performance of funeral rites and to preserve the continuance of one's lineage. A *Dattak Homam* made the relationship legally valid and gave full rights to name and inheritance to the son.

Foster care provides temporary substitute care for children. It is different form adoption where the child severs all ties with his own natural parents. In foster care, the child is placed in another family for a short or extended period of time depending on the circumstances. The child's own parents usually visit regularly and eventually after rehabilitation the child may return home. When the child is undergoing a temporary crisis (like the death of a parent or sudden illness, or even during large scale natural calamities like earthquakes or cyclones), children experience a lot of stress. They may need to be removed from their natural home to prevent their emotional abuse or neglect. These children can be placed in foster families till the crisis is over or they are adopted.

PRESENT STATUS OF ADOPTION

The traditional approach for care of destitute, neglected, abandoned, marginalized children and children in especially difficult circumstances was institutionalization. This approach resulted in children being separated from the family environment. Moreover, the peril of exploitation in institutional care, like the well documented physical and sexual abuse of children and the rather difficult task of monitoring care within homes has added to the danger of the institutional care. During the last few decades, the significant role that the family plays in the child's nurture and his or her physical, psychological, mental and social and psychological development has been increasingly realized. Every child has a right to a family. This can be achieved by strengthening the family as a unit, by providing counseling and support services, especially financial aid and education. When the child's own family cannot look after him or her, substitute family-based care has to be arranged. Thus, the trend has changed from institutionalized to family-based care, like adoption and foster care. Even the latter is to be considered as temporary measure until the child can be rehabilitated with his or her natural or adoptive family. *Special needs children* waiting for adoption include those of school age, part of a sibling group, members of ethnic communities and minorities, or have physical, emotional or developmental needs. Most children placed for international adoption have histories of poverty and social hardship in their home countries; many adopted from orphanages and other institutional settings are older children or *Children with Special Needs.*

While the *Right to be Adopted* as a fundamental right cannot be debated, it does not disqualify the fact that the *Right to be Cared For* by biological parents is the basic right—which requires governments to offer support and aid to families to care for their children—in terms of education and health-care at the very least.

LEGAL PERSPECTIVE ON ADOPTION

- Adoption is legally defined as the process through which the adopted child is permanently separated from his biological parents and becomes the legitimate child of his adoptive parents with all the rights, privileges and responsibilities that are attached to the relationship.
- Adoption in the earlier times were *parent-centered*—the needs of the parents being the primary consideration. Beginning from the 60s, changes have taken place at the social, legal and practice levels of adoption.
- With *The National Policy for Children 1972, The United Nations Declaration on the Rights of the Child 1959* and most importantly, *The United Nations Convention on the Rights of the Child 1989*, which spawned in its wake *The Juvenile Justice (Care and Protection of Children) Amendment Act, 2006*, the focus on adoption has now clearly shifted from the needs of the parents to the rights of the child to a family.
- **Central Adoption Resource Agency** Adoption in India is governed by a set of guidelines notified by Government of India vide *Central Adoption Resource Agency (CARA)*. CARA is the nodal body for adoption of Indian children and is mandated to monitor and regulate in-country and intercountry adoptions. CARA primarily deals with adoption through its associated/recognized adoption agencies. Guidelines issued by CARA, as notified by the Central Government under Section 41(3) of the Juvenile Justice (Care and Protection of Children) Act, 2000, are applicable to all matters relating to adoption.

Salient Features of Legal System for Adoption in India
- The child's best interest shall be of prime importance while deciding any placement

> **BOX 1** Additional eligibility criteria for prospective adoptive parents (PAPs)
>
> 1. No child may be given in adoption to a couple unless they have at least 2 years of stable marital relationship.
> 2. Couples in live-in relationship are not eligible to adopt a child.
> 3. To adopt a child in the age group of 0–3 years, the maximum composite age of the PAPs should be 90 years wherein the individual age of the PAPs should not be less than 25 years and more than 50 years.
> 4. To adopt children above 3 years of age, the maximum composite age of the PAPs should be 105 years wherein the individual age of the PAPs should not be less than 25 years and more than 55 years.
> 5. In case a single PAP desires to adopt, he or she should not be less than 30 years of age and shall not be above the age of 50 years.
> 6. The maximum age shall be 45 years to adopt children in the age group of 0–3 years and 50 years for adopting children above 3 years.
> 7. The PAPs should have adequate financial resources to provide a good upbringing to the child.
> 8. The PAPs should have good health and should not be suffering from any contagious or terminal disease or any such mental or physical condition, which may prevent them from taking care of the child.
> 9. Adoption of a second child is permissible only when the legal adoption of the first child has been finalized but this is not applicable in case of siblings.
> 10. An unmarried or single male person is not permitted to adopt a girl child.

> **BOX 2** Recommended screening checklist for adoption
>
> 1. Vision
> 2. Hearing
> 3. Growth charting
> 4. Immunizations
> 5. Developmental evaluation
> 6. Complete blood count for hematological disorders
> 7. Urinalysis
> 8. Stool examination and culture for intestinal infestations
> 9. HBsAg
> 10. VDRL
> 11. Hepatitis C
> 12. HIV ELISA (PCR if child is less than 6 months of age)
> 13. Mantoux test
> 14. Thyroid
> 15. SGOT, SGPT, bilirubin and alkaline phosphatase levels
> 16. G6PD and other newborn screening if available
> 17. Psychological health.

- Preference shall be given to place the child in adoption within the country
- Adoption of children shall be guided by a set procedure and in a time-bound manner
- No one shall derive any gain, whether financial or otherwise, through adoption.

Persons Competent to Adopt

The court may allow a child to be given in adoption (a) to a person irrespective of marital status; or (b) to parents to adopt a child of same sex irrespective of the number of living biological sons or daughters; or (c) to childless couples. Additional eligibility criteria for *prospective adoptive parents (PAPs)* are listed in **Box 1**.

ROLE OF THE PEDIATRICIAN

Preadoption

Pediatricians can help PAPs evaluate health and developmental history of the child, available background information from birth, and the child's current medical condition; and thus, assess actual and potential problems or risks that these children may have. This evaluation may lead to many unanswered questions that need to be documented for further examination. Growth charts relevant to the child's ethnicity need to be used to assess anthropometric parameters. Examination findings may help to ascertain dysmorphic features, growth, development and systemic illness. A candid and easy-to-understand interpretation of this information should be shared with the PAPs, in a nonpartisan manner. It is not the pediatrician's role to judge the advisability of a proposed adoption. It is appropriate and necessary that the prospective parents and any agency involved be apprised clearly and honestly of any special health needs detected now or anticipated in the future. Parents need to be counseled about creating the right and developmentally appropriate environment for the child.

Postadoption

Pediatricians should undertake a comprehensive assessment of the child's health, growth and development. Significant number of children would have acute or chronic medical problems, including growth deficiencies, developmental delay, feeding difficulty, sensory difficulties, attachment disorders, anemia, congenital disorders and birth defects, hepatitis B and C infections, common respiratory and gastrointestinal infections, skin infections, tuberculosis, strabismus, or intestinal infestations. Acute illness and infections should receive immediate medical care. Immunizations are frequently incomplete and need to be completed. Lack of secure attachment relationship and maternal deprivation in early childhood makes adoptive children vulnerable to psychosocial problems. Psychological disorders, especially in older children, who have witnessed conflict—domestic or social, and show signs of *post-traumatic stress* should be looked for and attended to. **Box 2** provides a recommended checklist.

Postadoption Follow-up

Adoptive parents may need guidance regarding all aspects of infant and child care and many need extra-assistance during the early adjustment period. Young children often learn their new language at a remarkable rate and adapt to their new surrounding without difficulty. Older children may be disoriented by their disruption in their familiar routines like new foods, new residence, a new language and change in weather. Dramatic catch-up growth in height, weight and head circumference is common in the first 6–12 months following the adoption. Over time, developmental delays and behavioral problems may emerge indicating the need for further psychological and educational intervention. Families should be encouraged to speak freely and repeatedly about adoption with the child, beginning in the toddler years and continuing through adolescence. Various stories from folklore as well as instances

known to the child and family may be freely discussed. Thus, the child is familiarized with the concept of adoption and looks at it in a positive light and is better prepared to accept it when told about his own adoption. It is necessary that the child be told about his own adoption by the adoptive parents rather than hearing about it from others. Hence, it is better done as early as possible. Indian families place high value on heredity. Adopted children may face resentment and nonacceptance from the extended family members. Extended family counseling to help alleviate prejudice may be necessary. The pediatrician needs to treat the parents as well as the child with empathy and patience. Most adopted children and families adjust well and lead healthy productive lives. Disruption rates are higher among children adopted from foster care homes, which may be associated with older age at the time of adoption, a history of multiple placements or a history of exposure to trauma and abuse prior to adoption. Great care needs to be paid to preparation of adoptive parents, and ensuring their availability of a full range of postadoption services; including physical health, mental health and developmental services for the adopted children.

MORE ON THIS TOPIC

Bajpai A. Right to Family Environment: Adoption and Other Non-Institutional Services. Child Rights in India-Law, Policy and Practice: Oxford University Press; 2004.

Fazel M, Stein A. The mental health of refugee children. Arch Dis Child. 2002;87:366-70.

Holloway, JS. Outcomes in placements for adoption or long-term fostering. Arch Dis Child.1997;76:227-30.

Inder Singh vs Kartar Singh, All India Reporter (AIR) 1966. Punj 258.

IN A NUTSHELL

1. Adoption is legally defined as the process through which the adopted child is permanently separated from his biological parents and becomes the legitimate child of his adoptive parents with all the rights, privileges and responsibilities that are attached to the relationship.
2. CARA is the nodal body for adoption of Indian children and is mandated to monitor and regulate in-country and intercountry adoptions.
3. The child's best interest shall be of prime importance while deciding any placement.
4. Preference shall be given to place the child in adoption within the country.
5. Adoption of children shall be guided by a set procedure and in a time bound manner.
6. No one shall derive any gain, whether financial or otherwise, through adoption.
7. Pediatricians can help *prospective adoptive parents (PAPs)* evaluate health and developmental history of the child, available background information from birth and the child's current medical condition.
8. Pediatricians can assess actual and potential problems or risks that these children may have.
9. Psychological disorders, especially in older children, who have witnessed conflict—domestic or social, and show signs of *post-traumatic stress* should be looked for and attended to.
10. Families should be encouraged to speak freely and repeatedly about adoption with the child. It is necessary that the child be told about his own adoption by the adoptive parents rather than hearing about it from others.

Chapter 50.6
Rights of the Child
Swati Y Bhave, Piyush Gupta

Convention on the Rights of the Child (CRC), an International treaty established on January 26, 1990 by the United Nations General Assembly, defines a *child* as a person below the age of 18 years, unless the relevant laws recognize an earlier age of majority. In some cases, countries are obliged to be consistent in defining benchmark ages—such as the age for admission into employment and completion of compulsory education; but in other instances the convention is unequivocal in setting an upper limit—such as prohibiting life-imprisonment or capital punishment for those under 18 years of age.

The *CRC* is a set of international standards and measures intended to protect and promote the well-being of children in society. The convention, in a sense, is a means of empowering children and creating an environment in which all children are able to live securely and realize their full potential of life. There are four basic rights of children.

A. The Right to Survival
This includes right to life, the attainable standard of health, nutrition and an adequate standard of living. It also includes right to a name and a nationality. These rights seek to ensure that children have nutritious food, potable drinking water, a secure home and access to health facilities. Every child has the right to live with his or her parents and the child shall not be separated from parents against his or her will except when such separation is necessary in the best interests of the child. The child also has the right to maintain contact with both parents if separated from one or both.

B. The Right to Protection
Every child has a right to freedom from all forms of exploitation including sexual exploitation, abuse, prostitution and involvement in pornography and drug abuse, inhuman or degrading treatment and neglect by parents or others responsible for care of children. Every child:
- Has the right to special protection in a situation of emergency and armed conflicts,
- Has the right to special protection when seeking refugee status or is a refugee,
- When disabled, has the right to special care, education and training,
- Has the right to be protected from work that threatens his or her health, development and education, and
- Has the right to the highest standard of health and medical care attainable.

C. The Right to Development
These rights include the right to education, support for development and care during early childhood, and the right to have adequate social security. It is the State's duty to ensure that primary education is free and compulsory. Children can enjoy their own culture, practice their religion and communicate in their own language. They have a right to social security, leisure, and play.

D. The Right to Participation
Children have the right to express their opinions and views. They have the right to obtain information, and the right to freedom of thought and expression.

CONVENTION ON THE RIGHTS OF THE CHILD

Convention on the Rights of the Child constitutes a common reference against which progress in meeting human rights standards for children can be assessed and results compared. Governments are obliged to bring their legislation, policy and practice into accordance with the standards in the Convention; to transform the standards into reality for all children; and to abstain from any action that may preclude the enjoyment of those rights or violate them.

The international community monitors and supports progress on the implementation of the Convention. The Committee on the Rights of the Child, an internationally elected body of independent experts that sits in Geneva to monitor the Convention's implementation, requires governments that have ratified the Convention to submit regular reports on the status of children's rights in their countries. The Committee reviews and comments on these reports and encourages States to take special measures and to develop special institutions for the promotion and protection of children's rights. Where necessary, the Committee calls for international assistance from other governments and technical assistance from organizations like UNICEF.

The new vision of the child in the Convention. The Convention provides a universal set of standards to be adhered to by all countries. It reflects a new vision of the child. Children are neither the property of their parents nor are they helpless objects of charity. They are human beings and are the subject of their own rights. The Convention offers a vision of the child as an individual *and* a member of a family and a community, with rights and responsibilities appropriate to his or her age and stage of development. Recognizing children's rights in this way firmly sets a focus on the whole child. Previously seen as *negotiable*, the child's needs have become legally *binding rights*. No longer the *passive recipient* of benefits, the child has become the subject or *holder of rights*.

The Convention is in force in virtually the entire community of nations, thus providing a common ethical and legal framework to develop an agenda for children. At the same time, it constitutes a common reference against which progress may be assessed. Children's rights are not special rights, but rather the fundamental rights inherent to the human dignity of all people, including children. Children's rights can no longer be perceived as an option, as a question of favor or kindness to children or as an expression of charity. They generate obligations and responsibilities that we all must honor and respect.

The Convention on the Rights of the Child is the most widely and rapidly ratified human rights treaty in history. It has been accepted even by nonstate entities, e.g., the Sudan People's Liberation Army (SPLA), a rebel movement in Southern Sudan. To date only two countries, Somalia and the United States, have not ratified this celebrated agreement. Somalia is currently unable to proceed to ratification as it has no recognized government. By signing the Convention, the United States has signaled its intention to ratify—but has yet to do so.

CHILD RIGHTS IN INDIA

With more than a third of its population below the age of 18, India has the largest child population in the world. India has made some significant commitments towards ensuring the basic

Table 1 Constitutional provisions protect children in India

Articles of Indian Constitution	Contents
Article 15	Affirms the right of the State to make special provision for women and children.
Article 24	Provides that no child below the age of 14 years shall be employed to work in any hazardous employment.
Article 39(e) of the directive principles of state policy	Provides that children of tender age should not be abused and that they should not be forced by economic necessity to enter vocations unsuited to their age or strength.
Article 39(f)	Requires children to be given opportunities and facilities to develop in a healthy manner and in conditions of freedom and dignity, and that childhood and youth be protected against exploitation and moral and material abandonment.
Article 45 of the directive principles of state policy	Provides for free and compulsory education for all children until they complete the age of 14 years.
Article 21-A The Right of Children to Free and Compulsory Education (RTE) Act, 2009	Every child has a right to full time elementary education of satisfactory and equitable quality in a formal school which satisfies certain essential norms and standards. The Act came into effect on 1 April 2010.

rights of children. There has been progress in overall indicators: infant mortality rates are down, child survival is up, literacy rates have improved and school drop-out rates have fallen. But the issue of child rights in India is still caught between legal and policy commitments to children on the one hand, and the fallout of the process of globalization on the other. India was amongst the 61 countries who first signed the CRC on January 26, 1990, the opening day of the UN General Assembly session, India ratified the CRC in 1992.

Several constitutional provisions protect children in India **(Table 1)**. Various five year plans of India have progressively added more schemes for welfare and protection of child. Despite these laws, policies, and commitments, the actual situation for India's children vis-à-vis health, education, early childhood care, and protection is not satisfactory.

National Plan of Action on Children

The National Plan of Action includes improvement in child health, in the health of expectant mothers, reduction in malnutrition, provision of and access to safe drinking water, universal enrolment of children in schools, ensuring a minimum level of learning, reduction of disparities and conservation and protection of the environment, so that it is conducive to the health and well-being of children. The Plan gives special consideration to children in difficult circumstances. Activities under the Plan include strengthening of the existing primary health-care infrastructure, consolidation and maintenance of levels of immunization coverage, stepping up immunization where coverage is low, polio eradication through immunization, ensuring essential

supplies and drugs, training of doctors and paramedical health workers, educating women and girls on safe motherhood, providing primary education facilities in unserved areas, providing child care services, and community mobilization and involvement.

National Charter for Children

Government of India announced a new draft *National Policy and Charter for Children, 2001*. This policy intends to remove the difficulties in our society, related to all issues affecting children's rights. The policy further aims to awaken the conscience of the community, to protect children from violation of their rights, and strengthening the family, society and the nation. This policy describes the steps to be taken by State and community to ensure that every child enjoys his or her rights as described in the *Convention on Rights of the Children*.

The National Commission for Children

The National Commission for Protection of Child Rights (NCPCR) was setup in March 2007 under an Act of Parliament. The Commission's mandate is to ensure that all laws, policies, programs, and administrative mechanisms followed in India are in consonance with the child rights perspective as enshrined in the Constitution of India and also the UN Convention on the Rights of the Child. The Commission focuses on the following tasks:

- To build public awareness and create a moral force in the country to stand by children and protect their rights.
- To look at the gaps in the policy framework and the legal framework and make recommendations to see that rights-based perspective is adhered to by the Government, while it makes its policies.
- To take up specific complaints that come up before it for redressal of grievances and also take up *suo moto* notice, summon the violators of child rights, get them presented before the Commission and recommend to the Government or the Judiciary, action based on an inquiry.
- To arm itself with proper research and documentation on various issues related to child welfare including health.

National Initiative for Protection of Children

The National Initiative for Child Protection (NICP) is a campaign initiated by Ministry of Social Justice and Empowerment. NICP aims to place child's rights on every agenda through partnership with allied systems for child protection and promotion of child's rights. The allied systems are police, health-care system, justice (juvenile) system, education system, transport system, labor department, media, department of telecommunications, corporate sector, elected representatives, and all of us. NICP will be implemented at district levels through state governments. It will design a curriculum that will be incorporated into the various training programs of academic institutions of the allied systems.

The Integrated Child Protection Scheme (ICPS)

This is a centrally sponsored scheme run by the Ministry of Women and Child Development aimed at building a protective environment for children in difficult circumstances, as well as other vulnerable children, through Government-civil society partnership. ICPS brings together multiple existing child protection schemes of the Ministry under one comprehensive umbrella, and integrates additional interventions for protecting children and preventing harm. ICPS, therefore, would institutionalize essential services and strengthen structures, enhance capacities at all levels, create database and knowledge base for child protection services, strengthen child protection at family and community level, ensure appropriate intersectorial response at all levels. The scheme plans

to setup a child protection data management system to formulate and implement effective intervention strategies and monitor their outcomes.

Juvenile Justice Act, 2000

The Government of India enacted the *Juvenile Justice Act* in 1986. After India ratified the UNCRC in1992 there was a need felt to rewrite the law. *The Juvenile Justice Care and Protection of the Child Act* was enacted in 2000. The Act defines a child or juvenile as a person under 18 years of age. The Act aims to target two groups: (1) Children in need of care and protection; and (2) Juveniles in conflict with law. The Act calls for establishment of the *Juvenile Justice Boards (JJBs)* for adjudication and disposition of matters related to juveniles; and *Child Welfare Committees (CWC)* to take care of children in need of care and protection.

Child Line

This is a national helpline for children in distress. It is India's first 24 hours service for children. It operates through a national toll free number 1098 and responds to the urgent and emergency needs of children such as medical assistance, shelter, protection from abuse and exploitation, assistance in child missing cases, repatriation, sponsorship, etc.

MORE ON THIS TOPIC

Child rights in India and status of children in India. From: http://infochangeindia.org/agenda/child-rights-in-india/status-of-children-in-india.html. Accessed December 8, 2014.

CRC-Convention on Rights of the Child. From: http://www.unicef.org/crc/index_30229.html. Accessed December 8, 2014.

Juvenile Justice Care and Protection of Children Act in India. From: http://www.childlineindia.org.in/Juvenile-Justice-Care-and-Protection-of-Children-Act-2000.htm. Accessed December 8, 2014.

The Integrated Child Protection Scheme (ICPS). Ministry of WCD, Govt of India. From: URL: http://wcd.nic.in/icpsmon/home1.aspx. Accessed December 8, 2014.

IN A NUTSHELL

1. United Nations General Assembly defines a "child" as a person below the age of 18 years.
2. Convention on the Rights of the Child (CRC), an International treaty established in 1990, recognized 4 basic rights of children:
   a. The Right to Survival
   b. The Right to Protection
   c. The Right to Development
   d. The Right to Participation
3. These rights are binding to the nations; children are not mere passive holders of these rights.
4. Despite constitutional provisions for protection of children in India, the ground reality for their health, education, early childhood care, and protection is not satisfactory.
5. National Policy and Charter for Children, 2001 for India ensures that every child enjoys his/her rights as described in the Convention on Rights of the Children.
6. The Juvenile Justice Care and Protection of the Child Act, 2000 of India aims to target children in need of care and protection; and juveniles in conflict with law.

Section 51 COMMUNITY PEDIATRICS

Section Editor *Piyush Gupta*

Chapter 51.1

Indicators of Child Health

Piyush Gupta, Dhulika Dhingra

The health of a community can be readily assessed by the level of care given to its children. Indicators are markers of health status, service performance or resource availability defined to enable the monitoring of objectives, targets and performance. The World Health Organization (WHO) has come up with a large compendium of indicators covering various illnesses and population. A composite coverage index (CCI) has also been devised to assess coverage in maternal, newborn and child health (MNCH). It comprises of four intervention areas including family planning, maternal and newborn care, immunization, and treatment of sick children. In this chapter, however, we shall concentrate on indicators primarily related to child health.

Table 1 describes a selection of health indicators recommended by the WHO for use in national health programs and services related to child health. Important mortality indicators of child health are defined in **Box 1**.

Perinatal mortality rate (PNMR); neonatal mortality rate (NMR), Infant mortality rate (IMR); Post-neonatal mortality rate (PNMR); and Under-5 mortality rate (U5MR) are few of the well-known indicators of child health. Perinatal mortality and neonatal mortality reflect the health and care of women during pregnancy and perinatal period, whereas infant mortality has been described as one of the most sensitive indices of health and quality of living of a population. **Table 2** depicts the current under-5 mortality rate, IMR, and NMR for selected countries.

UNDER-5 MORTALITY RATE

Under-5 mortality rate (U5MR) refers to the probability of children dying between birth and attaining 5 years of age, per 1,000 livebirths, per year. It is also expressed as a sum of IMR and child mortality rate.

$$\text{U5MR} = \frac{\text{Number of deaths in children aged}}{\text{Total number of children born live in that year}} \times 1000$$

It is an indicator of the well-being of all children below the age of 5 years. It also reflects income and education of parents, the prevalence of malnutrition and disease, availability of clean water, efficacy of health services, and health and status of women. It is an appropriate indicator of cumulative exposure to risk of death during the first 5 years of life. U5MR is also useful to evaluate effectiveness of various public health interventions. Under-5

mortality fell worldwide from 146/1,000 in 1970 to 48/1,000 in 2012. However, the process has slowed down in the last few years. There are regional differences as well. South-East Asia accounts for 28% of all child deaths; another 40% under-5 deaths occur in Africa. According to WHO, India, along with other countries of South-East Asia constitutes a *high mortality region.*

More than 10 million children are still dying every year across the globe before they are 5 years of age in addition to 3 million stillbirths. Causes of deaths of under-5 children (2012) are shown in **Figure 1**. While prematurity, infections, and asphyxia together contribute to almost 85% of neonatal deaths; conditions responsible for most of postneonatal under-5 deaths include pneumonia, diarrhea, malaria, and measles. About 35% of deaths in children have one or more of the three underlying risk factors: underweight, micronutrient deficiency, and suboptimal breastfeeding. Undernutrition is the leading risk factor, causing 21% of deaths.

INFANT MORTALITY RATE

It is the number of infant deaths in an year in relation to 1,000 live-births in the same year. This is irrespective of the fact that some of those infants who died in this year might have been born in the last few months of the previous year.

$$\text{IMR} = \frac{\text{Number of deaths in children} < 1 \text{ year}}{\text{Total number of livebirths in the same year}} \times 1000$$

Infant mortality rate of a nation is a well accepted long-standing indicator of wellbeing of her children. A high IMR is indicative of unmet health needs and unfavorable environmental conditions. UN estimates show that the global IMR has decreased from 87 per 1,000 livebirths during 1975–1980 to less than 50 per 1,000 today. The current IMR in India is 40 per 1,000 livebirths (SRS, 2014). The declining trend in India over the last 100 years (**Fig. 2**) has been mainly due to reductions in post-neonatal deaths. This decline in IMR is attributed to: (i) improvements in the quality of life due to environmental measures; (ii) better facilities for early diagnosis and treatment and prevention of communicable diseases; (iii) better health delivery systems; and (iv) improvement in overall nutritional status. Developed countries have shown greater reduction in infant mortality as compared to child mortality; while in the developing countries, the situation is reverse.

There is a wide variation in morbidity and mortality pattern of different regions in India. Madhya Pradesh and Assam have the highest infant mortality of 54 and Goa has the lowest of 9 per 1,000 livebirths (SRS, 2014). Statewise IMR according to SRS, 2014 is depicted pictorially in **Figure 3A**.

Table 1 Indicators of child health

Type of indicator	Name of indicator	Definition	Uses	Format of presentation
Mortality	Infant mortality rate (IMR)	Number of deaths of infant under one year of age, in a given period of time, per 1,000 livebirths in the same period	Measurement of cause specific mortality can serve: 1. To establish the relative public health importance of the different possible determinants of death 2. To evaluate trends over time as a method of evaluating impact of intervention 3. To select place and program interventions	Graphically
	Under-5 mortality rate	Probability of children dying between birth and their 5th birthday, expressed per 1,000 children born alive	Measurement of cause specific mortality can serve: 1. To establish the relative public health importance of the different possible determinants of death 2. To evaluate trends over time as a method of evaluating impact of intervention 3. To investigate the circumstances surrounding the deaths of children for devising effective action to decrease child mortality 4. To investigate reason for differing rates of infant and child mortality among geographical areas and 5. To evaluate the effectiveness of specific public health interventions in controlled settings	Graphically
Nutrition	Stunting prevalence	Proportion of pre-school children (less than 5 years) below-2 standard deviations (-3 standard deviations for severe stunting) from the median height for age of WHO reference population	To measure cumulative deficient growth associated with long-term factors including: i) chronic insufficient dietary intake, ii) frequent infection, iii) poor feeding practices over a sustained period, and possibly, iv) low socio-economic status of the household	Classified as low, medium, high and very high for the prevalence range of < 20%, 20–29%, 30–39%, and ≥ 40%, respectively
	Underweight prevalence	Proportion of pre-school children (less than 5 years) below-2 standard deviations (-3 standard deviations for severe underweight) from the median weight for age of WHO reference population	To define the overall magnitude of malnutrition and its changes over time. It does not, however, distinguish between current and more chronic determinants of malnutrition	Classified as low, medium, high and very high for the prevalence range of < 10%, 10–19%, 20–29%, and ≥ 30%, respectively
	Wasting prevalence	Proportion of pre-school children (less than 5 years) below-2 standard deviations (-3 standard deviations for severe wasting) from the median weight for height of WHO reference population	To measure current malnutrition resulting from failure to gain weight or actual weight loss. Wasting could be due to: i) inadequate food intake, ii) illness or infection, or iii) current poor feeding practices	Classified as acceptable, poor, serious and critical for the mean weight for height Z-score of Greater than -0.40,-0.40 to -0.69, -0.70 to -0.99, and not more than -1.00; respectively
	Night blindness prevalence	Proportion of children aged 2–6 years who are night blind	1. To determine the magnitude, severity and distribution of vitamin A deficiency 2. The indicator is also useful for the evaluation of intervention programs 3. Computed serially, it helps to monitor change in the status of vitamin A in the body	Classified as mild, moderate and severe to define a public health problem and its importance, at cut-off prevalence of less than 1%, 1–4% and ≥ 5%. respectively

Contd...

Contd...

Type of indicator	Name of indicator	Definition	Uses	Format of presentation
	Goiter prevalence rate	Proportion of children 6–11 years (preferably 8–10 years) of age with goiter of any grade	A total goiter rate (goiter grades 1 and 2) of 5% or more in primary children aged 8–10 years is a signal for a public health problem. When ultrasonography is used to provide a more precise measurement of thyroid volume the indicator becomes significant in monitoring iodine control programs where thyroid volumes are expected to decrease over time	Classified as mild, moderate, and severe to define IDD as a public health problem and its importance, at cut-off prevalence of 5–19.9%, 20–29.9% and > 29.9, respectively
	Exclusive breastfeeding	Proportion of infants less than four months (less than 120 days) of age who has received only breast milk and no other liquids or solids including water but excluding medicines or vitamin and mineral supplements in form of drops or syrups	1. To have a common measure to assess breastfeeding practice and 2. To evaluate the progress and effectiveness of promotional efforts	Presented in a tabular form against age of the mother, geographic areas and rural/urban setting
Immunization	Immunization coverage	Proportion of children immunized against diphtheria, pertussis, and tetanus (DPT3), poliomyelitis (OPV3), hepatitis B and measles before their first birthday (and yellow fever in countries with yellow fever risk)	To measure the performance of immunization program and to take corrective measures	The indicator should be presented geographically by: 1. Maps of coverage by district for OPV3, DPT3 and measles, 2. Maps of the difference in coverage between DPT3 and HBV3
	Neonatal tetanus incidence	Proportions of districts with neonatal tetanus (NNT) incidence rate less than 1 per 1,000 livebirths	The indicator is useful for: 1. Identifying high-risk districts or communities for NNT, 2. Monitoring routine coverage of neonatal control programs, and 3. Monitoring the impact of neonatal control programs	Presented in a tabular form by sex, age, group, month, year, district, place of birth and immunization status. Maps should also distribution of cases by district, TT2+ or PAB (protected at birth) coverage by district and where supplemental immunization was conducted
	Measles deaths	Annual number of deaths due to measles in children under 5 years of age. It can be estimated by the following formula: [infants surviving to 1 year of age] × [1- (vaccine efficacy × coverage by first birthday) × case fatality rate due to measles]	Useful for: 1. Monitoring the effectiveness of management as well as control measures against measles and 2. To identify areas in need of special attention	Presented with respect to total measles cases, case fatality rate, immunization coverage and the geographical area involved
Indicators for treatment of sick children	Oral rehydration therapy	Percentage of children under-5 with diarrhea in the preceding 2 weeks who received oral rehydration therapy and continued feeding		
	Care seeking for pneumonia	Percentage of children aged 0-59 months with suspected pneumonia (cough and dyspnea) who sought care from a health provider		

Causes of Infant Deaths

Main causes of infant mortality during the neonatal and post-neonatal periods are different. Majority of neonatal deaths are accounted for by low birthweight, infections, birth asphyxia, sepsis, and congenital anomalies; whereas postneonatal mortality occurs primarily due to infections (diarrhea, respiratory infections, vaccine-preventable diseases) and malnutrition.

Low birthweight (< 2,500 g) as a result of maternal malnutrition, decreased spacing between births, large family size, and a high fertility rate is one of the prime factor resulting in high infant mortality. Non-practicing of exclusive breastfeeding, noncompliance with immunization on account of illiteracy, ignorance, cultural and social beliefs pose the greatest risk of deaths to the infant. Finally, poverty, poor standards of living,

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BOX 1 Mortality indicators of child health

1. *Infant Mortality Rate*
   Number of infant dying between birth and exactly 1 year of age expressed per 1,000 livebirths, per year.
2. *Neonatal Mortality Rate*
   The number of deaths among livebirths during the first 28 days of life per 1,000 livebirths, per year.
3. *Early Neonatal Mortality Rate*
   The number of child deaths less than 7 days of life expressed as per 1,000 livebirths in that reference year.
4. *Late Neonatal Mortality Rate*
   The number of child deaths between 7 and 28 completed days of life expressed as per 1,000 livebirths in that reference year.
5. *Postneonatal Mortality Rate*
   The number of child deaths of 29 days to less than 1 year of age expressed as per 1,000 livebirths in the reference year.
6. *Perinatal Mortality Rate*
   The number of deaths of fetus after 28 completed weeks of gestation plus the number of early neonatal deaths per 1,000 total births, per year.
7. *Stillbirth Rate*
   The number of stillbirths per 1,000 births (live and stillbirths) during the reference year.

Table 2 Indicators of Child Mortality in Selected Countries (2014)

Country	Under-5 mortality rank	Under-5 mortality rate (per 1,000 LB)	Infant mortality rate (per 1,000 LB)	Neonatal mortality rate (per 1,000 LB)	Perinatal mortality rate* (per 1,000 TB)
Afghanistan	16	97	70	36	97
Angola	1	167	102	47	
Australia	167	4	3	2	5
Bangladesh	60	41	33	24	59
Bhutan	67	36	30	18	32
Brazil	118	14	12	8	17
China	122	13	11	8	31
Egypt	89	22	19	12	21
Ethiopia	39	64	44	28	41
Finland	185	3	2	1	4
France	167	4	4	2	7
Germany	167	4	3	2	6
Iceland	194	2	2	1	
India	47	53	41	29	64
Indonesia	76	29	25	14	21
Japan	185	3	2	1	3
Malaysia	142	9	7	4	9
Mali	7	123	78	40	50
Nepal	61	40	32	23	41
Niger	10	104	60	28	54
Pakistan	23	86	69	42	56
Singapore	185	3	2	1	4
Sri Lanka	134	10	8	6	14
Sweden	185	3	2	2	5
UK	160	5	4	3	8
USA	150	7	6	4	7
Zambia	21	87	56	29	56

Sources: UNICEF. State of the World Children, 2015; *Neonatal and Perinatal Mortality, Country, Regional and Global estimates 2007.
Abbreviations: LB, livebirth; TB, till birth.

inaccessibility to safe water and proper sanitation contribute in a compounded fashion.

Preventing Infant Deaths

Preventive measures have to be aimed at improving the nutritional status of the mother, providing good and essential antenatal care, safe delivery, essential newborn care, promotion of breastfeeding, immunization, early detection of illness (achievable by growth monitoring) and their management, family planning, efficient services for reproductive and child health, provision of safe water, sanitation, improving the social and economic condition of the people and providing health education to the receptive audience. Pediatrics as such is a preventive medicine and prevention starts not after birth but before birth, in utero, and even before pregnancy when prospective mothers are counseled. On a national level, the child health policy needs to be followed politically, emotionally and with national commitment to the rights of children. Governments have to strive hard to implement policies for optimizing use of ORS, exclusive breastfeeding, universal immunization coverage, and achieving 100% female literacy. National health programs need constant reinforcement with involvement of NGOs and non-health sector.

NEONATAL AND PERINATAL MORTALITY RATE

Each year, of almost 27 million children born in the country, about 0.88 million die before they complete 1 month of life and over 1 million die before the reach their first birthday. NMR comprises almost 70% of the total IMR, in India. Though there has been steady decline in IMR over last few years, there is slow reduction in NMR. Any further reductions in IMR can only come from reductions in NMR. The greatest risk is within first 24-hour after birth when 25–45% of all neonatal deaths occur. Around 75% of newborn deaths occur within the first week. Reductions in deaths in the first week of life have shown the least progress.

The largest number of neonatal deaths (1.4 million per year) and stillbirths (1.3 million per year) occur in South-East Asia region. Major causes of neonatal deaths in this region are prematurity or low birthweight, infections and asphyxia. Other important causes of mortality are congenital anomalies, neonatal tetanus and diarrhea. Neonatal mortality is a measure of the intensity with which *endogenous factors* (birthweight, birth injuries) affect life. The high concentration of infant deaths in the early neonatal period with endogenous factors suggests the need to improve the antenatal and postnatal services to expectant mothers. However, neonatal mortality is the most difficult part of infant mortality to alter, because of the endogenous factors which are not sensitive to improvements in environmental conditions.

Indices related to neonatal and perinatal mortality are calculated as follows:

Neonatal mortality rate It is the number of neonatal deaths in relation to 1,000 livebirths per year.

$$NMR = \frac{\text{Number of deaths in neonate aged} < 28 \text{ days in an year}}{\text{Total number of livebirths in the same year}} \times 1000$$

Stillbirth rate (SBR) It is the number of stillborn infants (after 28 weeks of gestation) related to total number of births (both live and stillborns) during the same period. It is expressed in relation to 1,000 total births.
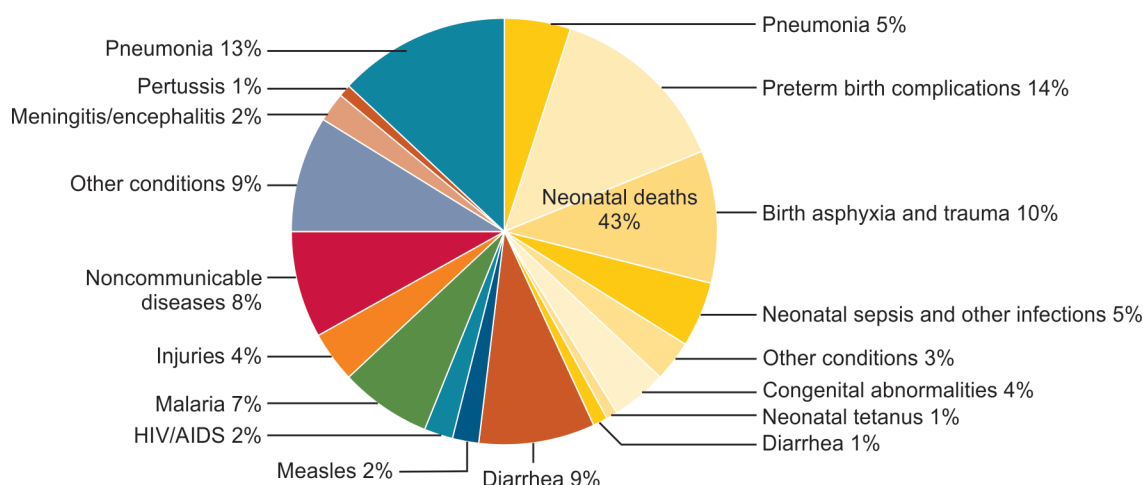
Figure 1 Global distribution of causes of death among children aged under-5 and in the neonatal period, 2012
From: Maternal, child and adolescent health (MCA) Report, WHO 2012-2013. Geneva: WHO; 2014. Reproduced with permission from the Publisher.
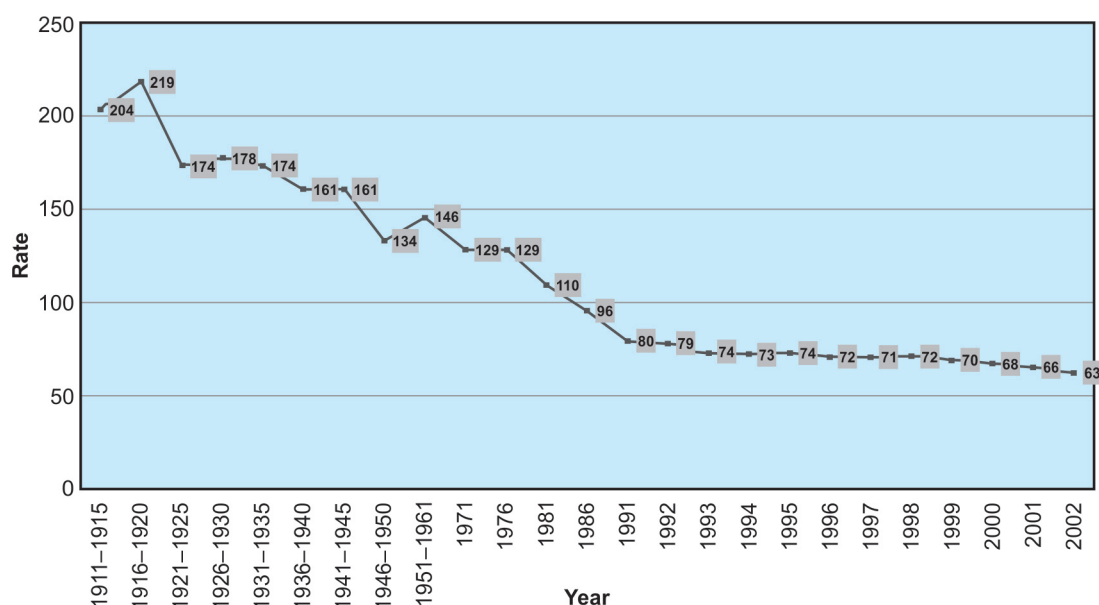
Figure 2 Decline of infant mortality rate in India in the last century

$$SBR = \frac{\text{Number of stillborn infants in an year}}{\text{Total number of births in the same year}} \times 1000$$

Perinatal mortality rate Number of deaths occurring in the perinatal period (includes stillbirths plus the deaths occurring in the first 7 days after birth) in a given year to the total number of births (live and still) in the same year. It is also expressed as rate per 1,000 total births. For the purpose of inclusion in this rate, the stillbirth or livebirths should be either (i) > 1,000 g in weight; (ii) > 28 weeks in gestation; or if (i) and (ii) are not available, should measure 35 cm or more in length at birth.

$$PNMR = \frac{\begin{array}{c}\text{Number of stillbirths + neonatal death}\\\text{during the first week of life in an year}\end{array}}{\text{Total number of births in the same year}} \times 1000$$

Statewise distribution of NMR, PNMR, and SBR for India is shown in **Figures 3B to D**.

HEALTH INDICES IN INDIA

Poor nutrition can result in increased susceptibility to infectious diseases and also has long-lasting negative cognitive and physical consequences including intellectual impairment, elevated risk of adult onset cardiovascular disease, and diabetes. In recent times, stunting has been singled out as key indicator for assessing child nutrition and its consequences. Similarly, exclusive breastfeeding is another important indicator estimated to prevent almost 13% of under-5 mortality. Immunization is also an important component of reducing under-5 mortality. Immunization coverage estimates are used to monitor coverage

Figures 3A to D Statewise distribution of: (A) infant mortality rate, (B) neonatal mortality rate, (C) perinatal mortality rate, and (D) stillbirth rate in India

Abbreviations: IMR, infant mortality rate; NMR, neonatal mortality rate; PNMR, post neonatal mortality rate; SBR, stillbirth rate; and SRS, sample registration survey.

Source: SRS Bulletin 2014; SRS Statistical Report 2013.

Table 3 Fertility, mortality, and other key health indicators, India

Fertility indicators	
Crude birth rate	21.4 (SRS Bulletin 2014)
General fertility rate	78.5 (SRS Statistical Report 2013)
Total fertility rate	2.3 (SRS Statistical Report 2013)
Gross reproduction rate	1.1 (SRS Statistical Report 2013)
Natural growth rate	14.4 (SRS Bulletin 2014)
Mortality indicators	
Crude death rate	7.0 (SRS 2014)
Infant mortality rate	40 (SRS 2014)
Neonatal mortality rate	28 (SRS Statistical Report 2013)
Early neonatal mortality rate	22 (SRS Statistical Report 2013)
Late neonatal mortality rate	6 (SRS Statistical Report 2013)
Post neonatal mortality rate	12 (SRS Statistical Report 2013)
Perinatal mortality rate	26 (SRS Statistical Report 2013)
Stillbirth rate	4 (SRS Statistical Report 2013)
Under-5 mortality rate	49 (SRS Statistical Report 2013)
Death rate for 5-15 years	0.7 (SRS Statistical Report 2013)
Maternal mortality ratio	178 (SRS Special Bulletin 2013)
Life expectancy at birth	Males 63.95 year (2011)
	Females 67.08 year (2011)
Immunization coverage	
BCG	87% (SOWC, UNICEF, 2015)
DPT 3 doses	72% (SOWC, UNICEF, 2015)
OPV 3 doses	70% (SOWC, UNICEF, 2015)
Measles	74% (SOWC, UNICEF, 2015)
Vitamin A supplementation, full coverage (%)	59% (SOWC, UNICEF, 2015)
Nutrition indicators	
Under-5 suffering from	
Underweight (weight for age < -2SD)	44% (SOWC, UNICEF, 2015)
Wasting (weight for height < -2SD)	20% (SOWC, UNICEF, 2015)
Stunting (height for age < -2SD)	48% (SOWC, UNICEF, 2015)

Abbreviations: SRS, sample registration survey; SOWC, state of the world children report.

Sources:
1. Govt. of India. SRS Special Bulletin on Maternal Mortality in India 2010-12, December 2013. Available at: http://www.censusindia.gov.in/vital_statistics/SRS_Bulletins/MMR_Bulletin-2010-12.pdf. Accessed January 1, 2015.
2. Govt. of India. SRS Bulletin, September 2014. Available at. http://censusindia.gov.in/vital_statistics/SRS_Bulletins/SRS%20Bulletin%20-Sepetember%202014.pdf. Accessed January 1, 2015.
3. Govt. of India. SRS Statistical Report December 2013. http://www.censusindia.gov.in/vital_statistics/SRS_Reports_2013.html. Accessed January 1, 2015.
4. UNICEF. State of the World's Children Report 2015. Available from: http://sowc2015.unicef.org. Accessed January 1, 2015.

of immunization services and guide disease eradication and elimination efforts. A brief outline of important health indices of India are summarized in **Table 3**.

COUNTDOWN TO 2015

Countdown to 2015 is a global movement of academics, governments and international agencies, professional organizations, donors, and non-governmental organizations. It uses country specific data to track, stimulate and support a country's progress towards achieving the health-related millennium development goals (MDG) particularly MDG 4 (reducing child mortality) and MDG 5 (improving maternal health). It focuses on coverage levels and trends for interventions proven to improve reproductive, maternal, newborn, and child health as well as critical determinants of coverage: health system functionality, health policies and financing. It examines equity in coverage across different population groups within and across countries. Since its inception, the countdown has emphasized the need to address inequities in maternal and child health as key strategy to improve health and survival.

MORE ON THIS TOPIC

Countdown 2008 Equity Analysis Group, Boerma JT, Bryce J, et al. Mind the gap: equity and trends coverage of maternal, newborn, and child health services in 54 countdown countries. Lancet. 2008;371:1259-67.

Levels and Trends in Child Mortality Report 2013. http://www.childinfo.org/files/Child_Mortality_Report_2013.pdf. Accessed December 15, 2014.

Singh PK, Rai RK, Kumar C. Equity in maternal, newborn and child health care coverage in India. Glob Health Action. 2013;6:2217-20.

Upadhyay RP, Chinnakali P, Odukoya O, et al. High neonatal mortality rates in rural India: what options to explore? ISRN Pediatr. 2012;2012:968921.

UNICEF. State of the World's Children/Reimagine the future. Available from: http://sowc2015.unicef.org. Accessed Jan 1, 2015.

World Health Statistics 2012. Indicator compendium. http://www.who.int/gho/publications/world_health_statistics/WHS2012_IndicatorCompendium.pdf. Accessed December 15, 2014.

Chapter 51.2
Environment and Child Health
Dhulika Dhingra, Piyush Gupta

Environment health deals with factors and circumstances in the surroundings which can influence human health and well-being. Children are exposed to serious health risks from environmental hazards including unsafe water, lack of sanitation, air pollution and exposure to chemical, wastes and toxins. Almost 3 million children under the age of 5 years die each year due to environment related diseases. Acute respiratory infections top this list killing 1.2 million children. More than 80% of diarrheal diseases (1.2 million) result due to poor sanitation and contaminated water. Children are more susceptible to environmental exposures owing to the immaturity of bodily systems and because of their large body surface area. MDG 7 aims at environmental sustainability and targets to have the proportion of people without sustainable access to safe drinking water and basic sanitation by 2015. The major domains of environment that influence child health are summarized in **Figure 1**.

AIR POLLUTION

Air pollution is defined as presence of substances in air in concentration and for duration that adversely affect human health. Air pollution can be *indoor* or *outdoor*. Principal pollutants and sources of outdoor and indoor pollution are summarized in **Table 1**.

Children comprise the largest subpopulation susceptible to the adverse effects of air pollution. Infants and children inhale and retain larger amounts of polluted air per unit of body weight than adults. Children also spend more time outdoors. Further in organogenesis there is a critical period of development when timing of exposure can be even more important for biological effects than its total dose because of higher rates of cell proliferation and changing metabolic capabilities. Studies have also suggested increase in childhood mortality following air pollution; a 10% increase in pollution may increase infant mortality by 1%. Children who are chronically exposed to silica, asbestos, coal dust, cement, because of their parent's occupation may suffer from pneumoconiosis. Particulates and to a lesser degree sulfates are positively associated with infant mortality; pollutants results in increased respiratory allergies, respiratory infections, and asthma. Air pollution can also result in low birthweight and intrauterine growth restriction (IUGR).
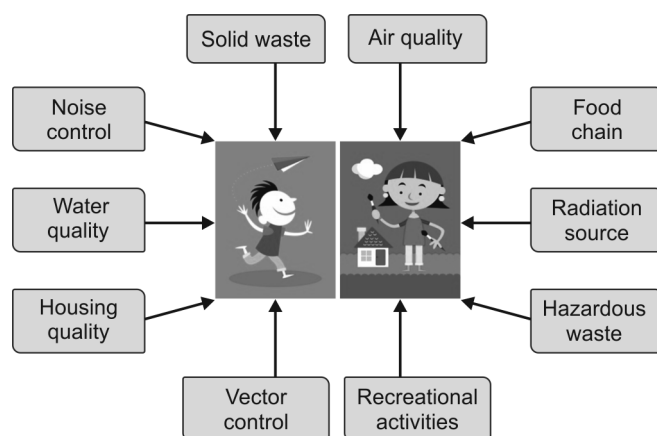
Figure 1 Major components of environment and health

Air pollution (due to nitric oxide, particulate matter < 2.5 μm, and elemental carbon) can have chronic and adverse effects on lung development in children 10–18 years of age. The health effects of important air pollutants are summarized in **Table 2**.

Indoor pollution in developing countries results from smoke emitted from solid fuel combustion in rural or semi-urban kitchens. Another important source of indoor pollution is tobacco smoke. Volatile substances used in furniture and paints also contribute. Vehicular pollution and large scale industrialization are leading causes of outdoor pollution. This has increased carbon dioxide emissions, the resulting greenhouse gas emissions have led to climate changes.

To improve air quality, heavy industries should be located away from high population areas. Industries that emit harmful emissions should have tall chimneys so that ground level concentrations may also be reduced. Efforts should be made for development and adoption of newer technologies to reduce fossil fuel use. There is an urgent need for the implementation of control programs to reduce the levels of pollutant emissions.

WATER POLLUTION

Water is essential for sustenance of life. It is used for drinking, cooking, bathing and washing, sanitation, agriculture, animal husbandry, and industrial purposes. Natural water is never pure from the chemical point of view; the impurities are derived from atmosphere or due to human activities. Pollutants in a water body include chemicals, pathogens, and changes in pH, electrical conductivity, temperature, and eutrophication. Chemical pollution primarily occurs because of persistent organic pollutants involving polychlorinated biphenyls (PCB), DDT, dioxins, endosulfan, etc. Most of them accumulate in fat tissues for long.

- *Point sources* of water pollution refer to contaminants that enter a water body from a single, identifiable source, such as a pipe or drain. This includes discharges from, for example, factories, sewage treatment plants or oil tankers. Point sources can be easily monitored and regulated.
- *Non-point sources* Pollution from non-point sources refers to diffuse contamination that does not originate from a single discrete source. Run-off water containing pesticides and fertilizers from areas of agricultural land are examples of non-point sources of water pollution. These are much more difficult to control.

Health Hazards
Health may be affected either directly by consuming contaminated water or indirectly through food chain and also by use of water for recreational, agricultural, trade and other purposes. Diseases related to water supply and caused by biological agents of disease are depicted in **Table 3**. The chemical pollutants include detergents, solvents, cyanides, heavy metals, minerals, organic acids, nitrogenous substances, dyes, pigments, bleaching agent, sulfates, ammonia, and many such other toxic substances. These pollutants are of diverse nature and are derived from industrial, trade and agricultural wastes. Acute toxic effects on human health by these pollutants presently are presumably of less concern than their long-term low-level exposures. Some of these substances are either known or suspected of having carcinogenic, mutagenic or teratogenic effects. Arsenic in drinking water is a major public health threat.

Control of Water Pollution
The Government of India has enacted several legislations to regulate water pollution by industries. Overexploitation of groundwater has

Table 1 Principal pollutants and sources of outdoor and indoor pollution

Principal pollutants	Sources
A. *Predominantly outdoor*	
1. Sulfur dioxide and particles	Fuel combustion, smelters
2. Ozone	Photochemical reactions
3. Pollens	Trees, grass, weeds, plants
4. Lead, manganese	Automobiles
5. Lead, cadmium	Industrial emissions
6. Volatile organic compounds	Petrochemical solvents, vaporization of unburned fuels
7. Polycyclic aromatic hydrocarbons	
B. *Both indoor and outdoor*	
1. Nitrogen oxides and carbon monoxide	Fuel burning
2. Carbon dioxide	Fuel burning, metabolic activity
3. Particles of vapors and combustion products	Environmental tobacco smoke, resuspension, condensation
4. Water vapor	Biologic activity, combustion, evaporation
5. Volatile organic compounds	Volatilization, fuel burning, paint, metabolic action, pesticides, insecticides, fungi, molds
6. Spores	Fungi, molds
C. *Predominantly indoor*	
1. Radon	Soil, building construction materials, water
2. Formaldehyde	Insulation, furnishing, environmental tobacco smoke
3. Asbestos	Fire retardant, insulation
4. Ammonia	Cleaning products, metabolic activities
5. Polycyclic aromatic hydrocarbons (PAH), arsenic, nicotine, acrolein	Environmental tobacco smoke
6. Volatile organic compounds (VOC)	Adhesives, solvents, cooking, cosmetics
7. Mercury	Fungicides, paints, spills or breakages of mercury containing products
8. Aerosols	Consumer products, house dust
9. Allergens	House dust, animal dander
10. Viable organisms	Infections

Source: Gupta P. Textbook of Preventive and Social Medicine. New Delhi; CBS: 2011.

particularly affected the availability of good quality drinking water in remote villages. Rain harvesting and groundwater recharge are being encouraged to make villages self-sufficient in their water needs. Individuals can contribute to control of water pollution by adhering to the following: (a) toxic products such as paints, automobiles oil, polishes and cleaning products should be stored and disposed off properly; (b) recycling should be encouraged, and (c) refrain from throwing the garbage into streams and lakes. Use environmental friendly household products such as toiletries, soap-based household cleaning material and washing powder as far as possible. Automobile oil should be reused. Vehicles should be serviced regularly and should be well maintained to prevent leakages of toxic fluids such as antifreeze and oil; and (d) actively conserve water by turning the tap off when you do not need running water, such as while brushing teeth. Avoid buying packaged water as far as possible. The best policy to adopt is to carry a bottle of water when you step out of the house. This not only reduces plastic waste but also reduces the cost.

NOISE POLLUTION

Noise is often described as *unwanted sound*. Still better, it can be defined as *wrong sound, in the wrong place, at the wrong time*. Sound is a vibration in a medium, usually air. Loudness of sound is measured in decibels (dB) and frequency or pitch is in hertz (Hz).

Sources Sources of noise that can affect a community include industry, transportation, construction activity, loudspeaker, horns, music system and public address systems. Night-time noise is a major disturbance to sleep above a level of about 40 dB. While sleep may not always be affected, adverse effects on daytime performance such as increased reaction time have been recorded. Noise in neonatal intensive care unit needs special mention. Ventilators, incubators, air compressors, humidifiers, air conditioners, discussion during ward rounds are sources of noise pollution in the neonatal units that can adversely affect the growing premature. It has been recommended that ambient noise should be below 45 dB and transient noise should be below 60 dB in neonatal units.

Adverse Effects

The deleterious effects of exposure to noise are of two types: *auditory* and *non-auditory*. The auditory effects include auditory fatigue and hearing loss. The non-auditory effects consist of interference with speech, annoyance, decrease in efficiency, and physiological changes like increase in heart rate, respiration, intracranial tension, blood pressure, and sweating. General symptoms such as giddiness, nausea, vomiting may also occur. Excess sound also interferes with sleep and is said to cause visual disturbances like distorted color perception and reduced night vision. Very loud noise (> 120 dB) can

Table 2 Some air pollutants and their effects on health

Pollutant	Effects related to short-term exposure	Effects related to long-term exposure
Particulate matter	Lung inflammatory reactions	Increase in lower respiratory symptoms
	Respiratory symptoms	Reduction in lung function in children
	Adverse effects on the cardiovascular system	Increase in chronic obstructive pulmonary disease
	Increase in medication usage	Reduction in lung function in adults
	Increase in hospital admissions Increase in mortality	Reduction in life expectancy, owing mainly to cardio-pulmonary mortality and probably to lung cancer
Ozone	Adverse effects on pulmonary function	Reduction in lung function development
	Lung inflammatory reactions	
	Adverse effects on respiratory symptoms	
	Increase in medication usage	
	Increase in hospital admissions	
	Increase in mortality	
Nitrogen dioxide	Effects on pulmonary function, particularly in asthmatics	Reduction in lung function Increased probability of respiratory symptoms
	Increase in airway allergic inflammatory reactions	
	Increase in hospital admissions	
	Increase in mortality	
Sulfur dioxide	Bronchial irritation, bronchospasm	
Polycyclic aromatic hydrocarbons	Penetrate lungs	Carcinogenic
Hydrocarbons	Eye irritation, odor	Carcinogenic
Carbon monoxide	Reduces oxygen-carrying capacity of blood	Affects central nervous system
Lead		Affects central nervous system, neurological effects

Source: Gupta P. Textbook of Preventive and Social Medicine. New Delhi; CBS: 2011.

Table 3 Diseases caused by biological agents related to water supply

S. No.	Group	Diseases
1.	*Water-borne diseases*	
	Diseases transmitted by water where water acts as a passive vehicle for infecting agent	Cholera, typhoid, bacillary dysentery, viral hepatitis, leptospirosis, giardiasis, gastroenteritis
2.	*Water-washed diseases*	
	Disease due to lack of water. Poor personal hygiene favors spread. Intestinal infections depend on lack of proper human waste disposal	Scabies, skin sepsis and ulcers, yaws, leprosy, lice, typhus, trachoma, conjunctivitis, bacillary and amebic dysentery, salmonellosis, worm infestations
3.	*Water-based diseases*	
	Infecting agents spread by contact or ingestion of water. An essential part of life cycle of agent takes place in aquatic animal	
4.	*Water-related diseases*	
	Transmitted by insects living close to water	Yellow fever, dengue, encephalitides, filariasis, malaria, onchocerciasis, sleeping sickness
5.	*Fecal disposal diseases*	
	Caused by infecting agents— by eating uncooked fish and other food	Clonorchiasis, diphyllobothriasis, fasciolopsiasis, paragonimiasis

Source: Gupta P. Textbook of Preventive and Social Medicine. New Delhi; CBS: 2011.

damage the cochlea irreversibly resulting in permanent hearing impairment, with the loss usually beginning at 400 Hz frequency (**Table 4**). Performance of simple tasks remains unaffected at noise levels as high as 115 dB, but complex tasks are disrupted at much lower levels. Loud noise can cause sleep disturbances and affect growth and feeding patterns in young infants and in rare cases may lead to sensorineural and mixed hearing loss.

Control measures Studies of continued exposure have shown that the risk of a rise in the hearing threshold of 25 dB doubles when the working lifetime exposure to noise increases from 85 dB to 90 dB. The standard recommendations on sound for the workplace is no more than 8 hours of exposure to 90 dBA, 4 hours to 95 dBA, or 2 hours to 100 dBA, with no exposure allowed to continuous noise above 115 dBA or impulse noise above 140 dBA. In nonoccupational settings, environmental noise is expressed as a day-night average sound level (DNL). US Environmental Protection Agency (EPA) has proposed a DNL of 55 dB and 45 dB, respectively during waking and sleep hours in residential neighborhoods, and 45 dB and 35 dB at day and night, in hospitals, respectively.

To regulate and control noise pollution, the Ministry of Environment and Forests, India has notified the Noise Pollution (Regulation and Control) Rules, 2000 under the Environment (Protection) Act, 1986, for prevention and control of noise pollution in the country. The notification aims to control noise in public places from various sources such as industries, construction activity, generators, loudspeakers, public address systems, music systems and vehicular horns.

RADIATION

Ionizing Radiation

It includes the natural cosmic and background radiation. Man-made sources include nuclear radiation and X-rays. Ionizing radiation is

Table 4 Health impacts of noise pollution

Noise level (decibels)	Impact
70-80	Uneasiness, tension, disturbance in sleep
80-85	Headache, loss of efficiency, annoyance
85-90	Hearing loss
90-100	Pain in terminal ears
100-120	Increased heartbeats, contraction of blood vessels
120-140	Impact on central nervous system, loss of memory
> 140	Hearing loss, pain, stress, abortions

mutagenic, carcinogenic, and teratogenic. Exposure to ionizing radiation during intrauterine period has been seen to be associated with mental retardation and reduced head circumference, risk being related to the dose as well as timing of exposure. Greatest risk is during 8–15 weeks of gestation. The role of ionizing radiation is well established in causation of premature aging, impaired fertility, and senile cataracts. Exposure to nuclear radiation results in cancers as early as 2–5 years after exposure. Approximately, one out of every 80 people exposed to 1 gray (Gy = 100 rad) will die from cancer and one in 40 people will be afflicted with cancer. Pediatric imaging is one of the important sources of exposure to ionizing radiation. Treating physician should justify use of such investigations and should prefer other modalities which reduce exposure including ultrasound and magnetic resonance imaging, where feasible.

Nonionizing Radiation

This includes ultraviolet radiation from the sun, electric radiation from artificial light sources, and natural and man-made electromagnetic fields (from electrical appliances, mobile phones, microwave, etc.). The increased use of electrical appliances has led to increased exposure of the population to electromagnetic rays which may increase the risk of some cancers. Recent research reveals harmful physiological, cellular and molecular effects of electromagnetic fields. A study found that children may face twice the risk of getting leukemia if they live near certain electrical sources such as power lines, hair dryers or black and white television sets. There are suggestions of possible negative health effects of weak nonionizing electromagnetic fields (EMFs), released by power lines, broadcast towers and other communication facilities and household appliances such as refrigerators, electronic blankets, shavers and toasters. It is believed that a child may be at more risk owing to thin skull bones and may even interfere with the activity of the nervous processes. The presence of high concentrations of positive ions, which give rise to electrical fields could interfere with growth mechanisms and lead to functional problems in the body. These ions enter the respiratory tract and nullify the regular growth of cells in the respiratory tract and lungs. Research on effects of mobile phones on child health is on high priority. It is likely that children using mobile phones may complain of poor attention span, decreased memory, increasing sleep disturbances, irritability and possibly brain tumors in later life.

Ultraviolet Rays

Ultraviolet rays are those nonionizing radiation in the electromagnetic spectrum with a wavelength shorter than that of visible light but longer than X-rays in the range of 10–400 nm. The short wavelength limit of the UV region is often taken as the boundary between the ionizing radiation spectrum and the non-ionizing spectrum. Ultraviolet rays can be classified into UVA (320–400 nm), UVB (290–320 nm) and UVC (100–290 nm). Apart from solar radiation, there are plenty of man-made sources which are capable of generating UV radiation including tungsten lamps, mercury vapor lamps, xenon lamps, hydrogen lamps, fluorescent

lightening, excimer laser, and dye laser. Apart from these lamps, microbiologists and pathologists use UV-lamps for germicidal purposes and disinfection. Such lamps are very efficient emitters of UV. Excessive exposure to UV rays may affect skin (pigmentation, premature aging, skin cancers), eyes (photokeratitis, pterygium, cataracts) and the immune system (suppressing cell-mediated immunity and enhancing risk of infections and suppressing response to vaccination).

Ozone layer of the stratosphere effectively absorbs all UVC and almost 90% of UVB rays. However, use of chlorofluorocarbons (used in refrigeration and metered dose inhalers) and methyl bromide have contributed to depletion of ozone layer aggravating the health hazards of UV rays. Ozone depletion may also result from increase in greenhouse gases. The major greenhouse gases include water vapor, carbon dioxide, methane and ozone. As heat is absorbed from the surface of earth, it gets absorbed by the greenhouse gases and is then re-radiated to the surface leading to increase in the surface temperature. Increase in carbon dioxide levels is one of the primary reasons for increase in greenhouse effect ultimately leading to ozone depletion.

However cells have evolved to deal with UV light. Sunbathing starts to redden our skin after about 12 hours. Tanning is also a defense mechanism, in which cells called melanocytes in lower layer are activated to produce deposits of brown melanin pigment. This compound absorbs UV and protects DNA. Sunscreen lotions also help in fighting against UV light, as it absorbs in the 290–320 nm region. Most skin cancers are easily noticed and cured, but melanoma may be fatal.

INDUSTRIALIZATION AND CHEMICAL POLLUTION

Industrialization and improvements in agriculture have made many positive contributions to health. However, industrial activities also carry the risk of adverse health consequences for the workforce and the general population, either directly through exposure to harmful agents or practices, or indirectly through environmental degradation. Residual chemicals are found in water, air and the food that we consume. Most of these chemicals do not have an excretory mechanism and persist in the adipose tissues. Heavy metals such as copper, nickel, mercury, lead may play a critical role in body's metabolism but their excess may lead to toxic effects including damage to cell membrane and cancers. *Dioxins* is another group of potential chemical pollutants resulting from smelting and incomplete combustion of solid waste and may affect human health by entering the food cycle. Studies have demonstrated *in utero* exposure to toxic chemicals may lead to neural tube defects. A study recruited 212 newborns born to mothers who had eaten Lake Michigan fish contaminated with polychlorinated biphenyls. Concentrations of polychlorinated biphenyls in maternal serum and milk at delivery were slightly higher than in the general population. The study revealed that prenatal exposure to polychlorinated biphenyls was associated with lower full-scale and verbal IQ scores at 2 years of age. The strongest effects were related to memory and attention. The most highly exposed children were three times as likely to have low average IQ scores and twice as likely to be at least 2 years behind in reading comprehension.

GLOBAL PLAN OF ACTION FOR CHILDREN HEALTH AND THE ENVIRONMENT

Children are our future and it is essential to have a healthy, safe and a clean environment to ensure their wholesome growth. Over the last 20 years there have been significant efforts in this direction. Two international conferences (2002, 2005) have reiterated their commitment towards control of environmental hazards to children.

The 3rd international conference was held at Busan, Korea in June 2009 where a global plan of action for child health and environment was devised. At Busan a road map was evolved involving the WHO and other government and nongovernmental organizations to devise measures to attain an environment conducive to the health of children and monitoring of goals achieved in this direction. The Busan pledge for action on child's health and environment is reproduced in **Box 1**.

GOVERNMENT OF INDIA INITIATIVES FOR ENVIRONMENT PROTECTION

The government has been trying to limit the damage to the environment since the 4th Five Year Plan (1968–73) when the Plan document recognized *the interdependence of living things and their relationship with land, air and water*. Since then, the environmental protection has been an important component of national development. The Government of India has over the years implemented a series of measures to protect the environment. In 1972, a committee on human environment was created. The Central Department of Environment was set up in 1980, which was converted into Ministry of Environment and Forests in 1985. The Ministry formulates environmental policies and legislations and implements the various programs for environment management.

The task of pollution control in India is complex. Increase in vehicular pollution coupled with poverty and the population boom puts tremendous pollution pressure on air and already scarce water and land resources. A comprehensive approach to pollution control is being undertaken based on the following principles: (a) Prevent pollution at source of generation; (b) each industrial unit should be specified the amount of pollutants that can be generated; (c) ensure that polluter is penalized for exceeding the limits; and (d) involve the public in decision-making. The government aims to achieve these objectives with the use of legislation, incentives, educational programs and information drives. The Central and State Pollution Control Boards are entrusted with the task of enforcing measures for pollution control.

IN A NUTSHELL

1. An unacceptable number of children are harmed or die unnecessarily from environment related diseases every day.
2. Developing countries bear a disproportionate share of the problem.
3. Exposures to environmental hazards are largely preventable.
4. Preventive interventions are effective in protecting children from adverse exposures.
5. Political commitment and resources are needed to move effectively from research to action and to reduce the number of preventable deaths and illnesses related to the environment.

MORE ON THIS TOPIC

Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med. 2004; 351:1057-67.

Preventing disease through healthy environments: Towards an estimate of environmental burden of disease. From: http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en/. Accessed on December 9, 2014.

Thornton JW, McCally M, Houlihan J. Biomonitoring of industrial pollutants: health and policy implications of the chemical body burden. Public Health Rep. 2002;117:315-23.

Water Pollution Control – a guide to the use of water quality. Management Principles. From: http://www.who.int/water_sanitation_health/resources/watpolcontrol/en/. Accessed on December 9, 2014.

WHO. Global Plan of Action for Children's Health and Environment. From: http://www.who.int/ceh/en/. Accessed on December 9, 2014.

Chapter 51.3
Lead Poisoning
Dhulika Dhingra, Piyush Gupta

Lead poisoning is one of the most common childhood diseases of environmental origin. Lead poisoning accounts for 0.6% of global disease burden, however patterns and sources of lead exposure and prevalence rates may vary from country to country. In a community based cross-sectional study in Indian children, the prevalence of elevated lead (≥ 10 µg/dL) was 67%.

ETIOPATHOGENESIS

Children absorb more lead than adults owing to their metabolic profile. A child may be exposed to lead by ingestion, inhalation (burning of waste, industrial activity, lead paint) and contact through skin (cosmetics). Ingestion is the most common route of poisoning (drinking water systems of lead pipes, herbal medications, lead food cans) (**Fig. 1**). A child's inquisitive behavior brings lead containing objects to his mouth and exposes the child to lead. They are at higher risk owing to exposure to lead during pregnancy, concomitant nutritional deficiencies and owing to longer years of life ahead and hence are more likely to develop late sequel of accumulated toxicity. Exposure in the intrauterine life can be particularly devastating as exposure in early life can reprogram genes leading to altered gene expression. Chronic lead intoxication may occur in children who eat nonedible substances (pica) and manifesting as pain in abdomen and resistant anemia.

Exposure to lead may also occur from old lead-based deteriorated house paint (in old houses) and dust and soil contaminated with lead such as from leaded gasoline, lead electrode plates from old automobile batteries, adulterated food, folk remedies, and broken lead typesets scattered around old printing establishments. Food may be adulterated with colored metallic salts or the black collyrium used as *surma* may contain a proportion of black oxide of lead.

CLINICAL MANIFESTATIONS

Lead is known to cause toxicity by inhibiting the ferrochelatase and aminolevulinic acid, two important enzymes of the heme biosynthesis pathway. Lead is also known to mimic calcium and hence interferes with calcium homeostasis disrupting cell signaling pathways. Virtually all neurotransmitters are affected by lead particularly the dopaminergic, cholinergic and glutamatergic systems. Lead toxicity has a wide range of toxicity profile in children. Manifestations may range from acute symptoms to subclinical manifestations. Although all systems may be affected, central and peripheral nervous systems are the principal organ systems to be affected. Acute lead toxicity may result from acute, high dose exposure to lead. It manifests as colic, pallor, decreased concentration, easy fatigability and constipation. Severe cases may also present with ataxia, seizures or coma. Wrist and foot drop have also been reported. Children who survive often have neurological sequel. Chronic toxicity is more common than acute toxicity but is more difficult to identify. Patients with prolonged exposure may present with resistant anemia, hyperuricemia and gout, hypertension, coronary artery disease, peripheral artery disease and impairment of immune and
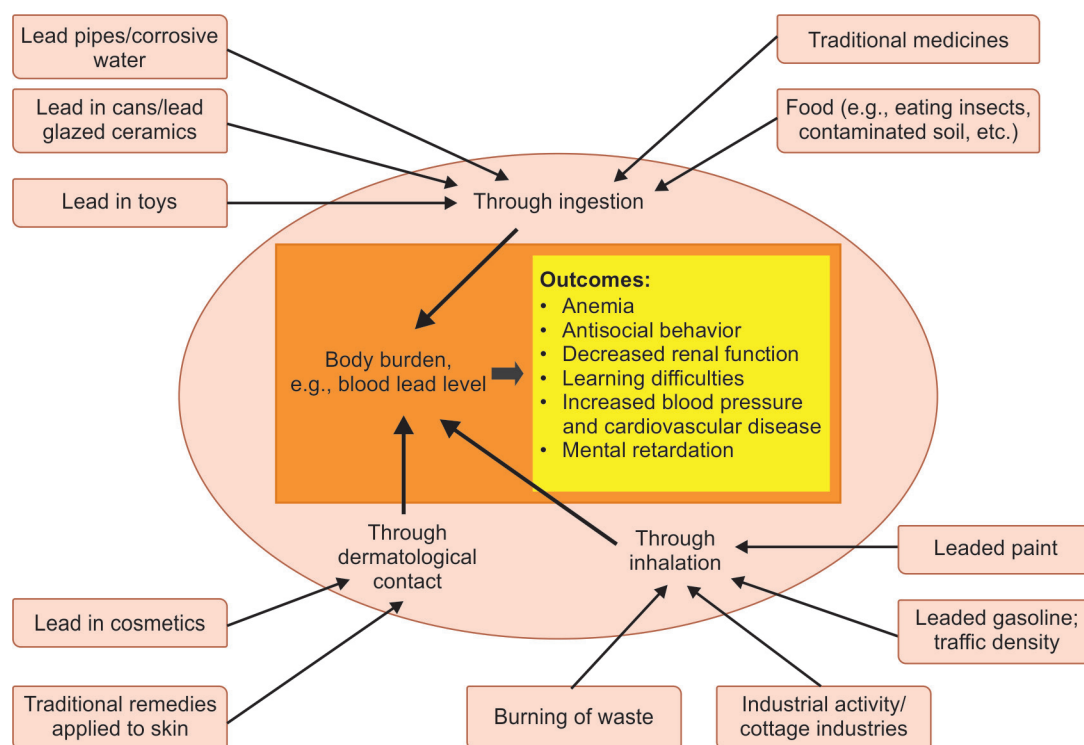
Figure 1 Sources of children's exposure to lead
Reproduced with permission from: WHO. Childhood Lead Exposure. Geneva: WHO; 2010. Available from: http://www.who.int/ceh/publications/leadguidance.pdf

reproductive functions. Children may present with poor scholastic performance, hearing difficulty, difficulty in sleeping and slowed body growth.

DIAGNOSIS

Lead poisoning is diagnosed by elevated levels of level in the blood. Levels of lead considered unsafe have changed over last 50 years. Levels more than 60 µg/dL was considered unsafe till the year 1960. This was reduced to 10 µg/dL in 1991. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) recommends elimination of the term *blood levels of concern*. This stems from various studies where children with low blood lead levels (BLL) presented with impaired intelligence quotients (IQ). Experts now use a reference level of 5 µg/dL to identify children with BLL that are much higher than most children's levels. New lower cut-off levels of lead would lead to more children being detected with lead exposure and hence early intervention may prevent severity of disease later. Gingival lead lines, radiographs of long bones, evaluation of lead in teeth and hair and urinary lead excretion of lead following provocation with chelation, microscopic evaluation of red cells for basophilic stippling are unreliable measures of BLL and not recommended for evaluation of lead exposure.

MANAGEMENT

Since it has now been long recognized that the damage caused by lead is by and large irreversible, management now focuses on primary prevention. In the pediatric office, counseling may begin in the prenatal period by counseling prospective parents. Parents should be informed about potential sources of lead exposure *viz* in house exposures, unsafe renovation practices and potential exposures noted in parental occupations and hobbies. Parents should be informed about the advantages of a well-balanced diet ensuring adequate amount of iron, calcium and vitamin C which prevent specific absorption of lead. Most important factor in managing a child with lead poisoning is reducing the exposure to lead. Some children may benefit from chelation. Dimercaprol (also known as British antilewisite or BAL) and calcium disodium edetate have been used as chelating agents. Succimer is an oral chelating agent approved by USFDA for chelation in children with BLL ≥ 45 µg/dL.

Medical Management of Symptomatic Lead Poisoning

Symptomatic lead poisoning (with/without encephalopathy) is a medical emergency. All such children should be managed in an intensive care unit. Therapy is usually started with dimercaprol (BAL) (75 mg/m^2 every 4 hourly IM). BAL may be stopped after 48 hours, while calcium disodium edetate is used for another 3 days but at a lower dosage of 1,000 mg/m^2/24 hours by continuous IV infusion. Maximum daily dose should not exceed 500 mg/kg. During this therapy the child's urine output, renal functions, liver functions and serum electrolytes have to monitored. Give a second course of edetate alone if blood lead rebounds to BLL of 45–69 µg/dL. A second course of edetate in combination with BAL is recommended for rebound lead level of more than 70 µg/dL. Wait for 5–7 days in between the two courses.

Medical Management of Asymptomatic Lead Poisoning

- *Blood lead levels ≥ 70 µg/dL* Asymptomatic children with BLL ≥ 70 µg/dL represent acute medical emergency and should be treated similar to symptomatic patients as above.
- *Blood lead levels 45–69 µg/dL* Only calcium disodium edetate is recommended for this group. The drug may be administered in a dose of 1,000 mg/m^2/24 hours by continuous IV infusion or in divided dosages. Treatment should not be extended beyond 5 days. A second course may be tried in patients with rebound increase in blood levels to 45 µg/dL if 5 days have elapsed after the first dose.
- *Blood lead levels 25–44 µg/dL* Chelation therapy is not recommended for this group of patients. Treatment in this group may be individualized. Patients in this group have to be monitored regularly and should be removed from all sources of lead exposure.

IN A NUTSHELL

1. Lead poisoning is one of the common childhood environmental diseases.
2. Primary prevention is the key to prevent morbidity.
3. The term blood levels of concern are a passé. Centers for Disease Control and Prevention (CDC) now recommends use of a reference level of 5 µg/dL to identify children with blood lead levels higher than most children's levels.
4. Gingival lead lines, radiographs of long bones, lead estimation in teeth and hair are unreliable and are not recommended for estimation of lead exposure.
5. Chelation is recommended for children with blood lead levels more than 45 µg/dL.

MORE ON THIS TOPIC

Carlisle JC, Dowling KC, Siegel DM, Alexeeff GV. A blood lead benchmark for assessing risks from childhood lead exposure. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2009;44:1200-8.

Chandran L, Cataldo R. Lead poisoning: basics and new developments. Pediatr Rev. 2010;31:399-405.

Kordas K. Iron, lead, and children's behavior and cognition. Annu Rev Nutr. 2010;30:123-48.

Koyashiki GA, Paoliello MM, Tchounwou PB. Lead levels in human milk and children's health risk: a systematic review. Rev Environ Health. 2010;25:243-53.

Ness R. Practice guidelines for childhood lead screening in primary care. J Pediatr Health Care. 2013;27:395-9.

Pfadenhauer LM, Burns J, Rohwer A, Rehfuess EA. A protocol for a systematic review of the effectiveness of interventions to reduce exposure to lead through consumer products and drinking water. Syst Rev. 2014;3:36.

Warniment C, Tsang K, Galazka SS. Lead poisoning in children. Am Fam Physician. 2010;81:751-7.

WHO. Childhood Lead Exposure. Geneva: WHO; 2010.

Chapter 51.4
Programs for Child Health
Amir Maroof Khan, Piyush Gupta

The children of today are the human capital of the future. As childhood is a vulnerable age group, it is pertinent that there are well established mechanisms at the programmatic levels to safeguard their health. Poor health during the early years may lead to a lifelong impairment. Apart from being a moral obligation, children's health is a valuable economic investment as it results in more productive adults further leading to favorable demographic changes in the long-term. Children born into poor families have poorer health as children, receive lower investments in human capital, and have poorer health as adults. Thus, policies and programs aimed at improving the health of children also contributes to breaking the intergenerational cycle of poverty in many countries (Belli PC 2005).

In the last few decades, a number of programs and strategies focused on reducing childhood mortality have been devised, implemented, evaluated and revised. A number of reasons have been proposed for this primacy of child health concerns at the global center stage (Reich MR, 1995). One was that, as infant mortality rates have been used as a proxy indicator for the country's health status it became the main target of governments of various countries across the globe. Even politicians face little opposition when investments in child health promotion are proposed. There was also enough scientific evidence that cost effective interventions are available that could save the lives of children.

PRE-PRIMARY HEALTH-CARE ERA—DISEASE CENTRIC APPROACH IN CHILD HEALTH PROGRAMS

The 1950s witnessed the global effort for eradication of malaria, which had an indirect effect on saving the lives of large numbers of children. Whereas this program ultimately could not achieve its objectives, another program at the global level, i.e., Smallpox eradication program met with tremendous success, with the world being declared free of smallpox in 1980. This pushed the policy makers towards the expansion of efforts towards other vaccine preventable diseases mainly affecting children particularly in the developing countries. World Health Organization launched the Expanded Program on Immunization (EPI) in May 1974 against six major vaccine preventable diseases, viz. diphtheria, pertussis, tetanus, tuberculosis, measles and polio. Thus, it is evident that disease-specific strategies have mainly guided the program level initiatives to reduce child mortality. The renewed thrust on vaccine preventable diseases exists even today with the advent and inclusion of newer vaccines such as for Hepatitis B, *Haemophilus influenzae* type b and rotavirus in national immunization schedules of many developing countries. Interest of donors, policy makers and administrators has been revived on this front in recent times with the launch of the Global Alliance for Vaccines and Immunization (GAVI) in 2000 with the aim of *immunization for all.*

MOVING TOWARDS COMMUNITY-BASED CARE IN CHILD HEALTH PROGRAMS

The Alma-Ata declaration at the International Conference of Primary Health Care approved the primary health-care as a much needed concept based on four principles; equitable distribution of health-care, intersectoral coordination, use of appropriate technology, and community participation. Linkages between health and development thus, were accepted. Even though it envisaged a paradigm shift from the curative to preventive aspects of medical science, it was opposed for being too idealistic and without specific measurable objectives. Rather than providing comprehensive primary care which seemed to be unrealistic and nonmeasurable, it was contemplated that those diseases which are responsible for the greatest number of deaths in the less developed nations and for which cost effective interventions are available should be targeted first. This has been called as the selective primary health care concept (Walsh and Warren, 1979). United Nations Children's Fund (UNICEF) translated these general goals into time bound specific objectives and came up with four key interventions for child health, i.e., growth monitoring, oral rehydration techniques, breastfeeding and immunization popularly known as GOBI (UNICEF, 1982). To these were later added female literacy, food supplementation and family planning. This can be termed as the first major global thrust at the policy making and programmatic level to improve the health of children in comprehensive manner.

Program on Control of Diarrheal Diseases (CDD) and Acute Respiratory Infections (ARI) control were other major child health related initiatives by WHO in the 1980s. Management of such cases in the community by community health workers and at home was introduced. Provision of ORS for preventing and managing dehydration and rational management of pneumonia with co-trimoxazole in the community settings proved to be effective strategies in reducing the child mortality rates. The involvement of community health workers from vaccination campaigns to community based disease management marked another big paradigm shift. Community health workers have become indispensable now under most of the child health related programs in most of the developing countries.

INTEGRATED APPROACH TO CHILD HEALTH

WHO reviewed diarrhea and ARI management strategies for children and identified a set of interventions, which gave direction to future research priority in shaping future child health programs. In the 1990s, research priorities evolved as efforts to develop a more integrated approach to case management both in the home and within the health system. The Integrated Management of Childhood Illness (IMCI) strategy jointly developed by WHO and UNICEF is an example of this approach. The conditions included in IMCI include the major communicable diseases as pneumonia, diarrhea, measles and malaria. As malnutrition has been reported to contribute to more than half of all childhood deaths, this condition is also included in IMCI. This strategy integrates the home-based care, health workers training in standard case management, and referral services. Breastfeeding, immunization, child feeding and nutrition also are included in this approach making it one of the most comprehensive strategy for childcare till date. The strategy was later extended to include the young infants and neonates below 2 months of age also and renamed as Integrated Management of Childhood and Neonatal Illnesses (IMNCI) in India.

The millennium development goals were established by the United Nations Summit in 2000. Even though MDG Goal 4 directly referred to reduction of child mortality, the other goals like reduction in poverty, reduction in deaths due to malaria, tuberculosis and HIV/AIDS, etc., were also important determinants of child health and survival (United Nations, 2000). The MDG Goal 4 (reducing child mortality) targeted a reduction in under-5 mortality rate by two-thirds between 1990 and 2015. Between 1990 and 2012, under-5 mortality declined by 47%, from an estimated rate of 90 deaths per 1,000 livebirths to 48. The global rate of decline has also accelerated in recent years—from 1.2% per annum during

1990–1995 to 3.9% during 2005–2012. Despite this improvement, the world is unlikely to achieve the MDG target of a two-thirds reduction in 1990 mortality levels by the year 2015. More countries are now achieving high levels of immunization coverage; in 2012, 66% of member states reached at least 90% coverage. In 2012, global measles immunization coverage was 84% among children aged 12–23 months. During 2000–2012, estimated measles deaths decreased by 78% from 562,000 to 122,000 (WHO, 2014).

In India also, child health care services moved from vertical child survival programs to a horizontal integrated program through the Child Survival and Safe Motherhood Program (CSSM) launched in 1992. Further inclusion of adolescent age group and reproductive health led to the launch of Reproductive and Child Health (RCH) Program in 1997. A wide range of initiatives were carried out under these programs; namely, immunization, control of ARI, control of diarrhea, vitamin A and iron supplementation, provision of essential newborn care, implementing exclusive breastfeeding till 6 months of age. This also included management of RTI/STI delivered through a Community Needs Assessment Approach (CNAA). In 2005, the modified RCH Program (RCH II) was put into operation with major addition being the inclusion of IMNCI.

Establishment of Newborn Care Facilities and Facility-based Integrated Management of Newborn and Childhood Illnesses (F-IMNCI)

F-IMNCI is the integration of the facility based care package with the IMNCI package, to empower the health personnel with the skills to manage newborn and childhood illness at the community level as well as at the facility. Facility based IMNCI focuses on providing appropriate skills for inpatient management of major causes of neonatal and childhood mortality such as asphyxia, sepsis, low birthweight and pneumonia. Neonatal mortality is one of the major contributors to the infant mortality. To address the issues of higher neonatal and early neonatal mortality, facility based newborn care services at health facilities have been emphasized. Setting up of facilities for care of sick newborn such as *special newborn care units* (SNCUs), *newborn stabilization units* (NBSUs) and *newborn care corners* (NBCCs) at different levels of health care has been put into operation.

Navjaat Shishu Suraksha Karyakaram

Effective newborn care is a crucial challenge that is faced by every health care setting dealing in maternal and child health. A key component is to equip the staff with appropriate knowledge and skill. The Ministry of Health and Family Welfare is addressing this through the launch of the *Navjaat Shishu Suraksha Karyakram* (NSSK). This program provides evidence-based knowledge in improving newborn heath, especially care at birth. The health provider after training will furnish all the required care at birth, identify and manage common complications, stabilize and refer or transfer newborns needing additional interventions. The objective of this new initiative is to have trained health personnel in basic newborn care and resuscitation at every delivery point.

Home-based Newborn Care

There is ample evidence to suggest that despite increasing number of institutional deliveries a substantial number of neonatal deaths occur at home. In cases where a baby is delivered at an institution and is discharged after 48 hours, the baby may still be at risk of illness in the first week to first month of life. In some cases, the mother would like to return home within few hours of delivery. The key provider of home based newborn care (HBNC) is accredited social health activist (ASHA), a key health worker under the National Rural Health Mission. Through a series of home visits,

she will provide newborn care by weighing the newborn, ensuring warmth and counseling the mother on temperature maintenance, initiating and supporting exclusive breastfeeding, promoting skin, eye and cord care and identifying early signs of sepsis and other illnesses.

UNICEF is working closely with National Rural Health Mission programs such as *Janani Suraksha Yojna* to encourage women to have institutional deliveries. The Ministry of Women and Child Development, the Government of India's nodal Ministry for the advancement of children and women, and UNICEF jointly developed the Country Program Action Plan (CPAP) for 2013–2017. The life cycle approach is the core principle of this effort. This is based on the acknowledgement that children and women face multiple deprivations at different stages of their life and that multidimensional problems need multipronged solutions.

CHILD NUTRITION PROGRAMS AND STRATEGIES

Malnutrition is an associated cause in about half of all deaths occurring among children in developing countries. There is a renewed effort to combat malnutrition among children and mothers by the WHO member states by agreeing to six global nutrition targets *viz.* reduction of stunting, wasting, maternal anemia, low birthweight, overweight and an increase in proportion of exclusive breastfed children up to 6 months of age to certain predefined targets by 2025. Social determinants of health approach will be used in scaling up and achieving equitable distribution regarding such evidence based, effective interventions that can help achieve multiple targets (WHO, 2014a).

One of the world's largest and most unique programs for early childhood development in India is the Integrated Child Development Services (ICDS) scheme which aims at provision of supplementary nutrition, immunization, preschool nonformal education, growth monitoring, health education and referral services (Ministry of Women and Child Development, Government of India, 2014). Another major initiative to combat undernutrition worth mentioning is the school meal program currently running in many countries by different names. Mid-day meal scheme in India aims at provision of school lunches thereby improving the nutritional status of children and their school enrollment and attendance.

In developing countries, about 40% of preschool children are estimated to be anemic which is aggravated by worm infestation, malaria and other infectious diseases. Iron-deficiency anemia leads to adverse effects on cognitive and motor development of the child. Strategies such as iron supplementation through weekly iron folic acid supplementation (WIFS) and regular deworming have therefore been incorporated in the child health programs of many developing countries.

Another micronutrient deficiency is vitamin A deficiency which is the leading cause of preventable blindness in children and increases the risk of disease and death from severe infections. Vitamin A deficiency is a public health problem in more than half of all countries, especially in Africa and South-East Asia, hitting hardest young children and pregnant women in low-income countries. Vitamin A supplementation has therefore been linked to national immunization programs in many countries (WHO, 2014b).

Iodine deficiency disorders affect children even before birth and leads to adverse fetal outcomes and also jeopardizes the mental health of the children. Since the 1980s, WHO has been at the forefront of providing technical support in the form of standards, guidelines, methodologies along with International Council for Control of Iodine Deficiency Disorders (ICCIDD) and UNICEF to set up sustainable national salt iodization programs to put an end to iodine deficiency disorders among children.

Nutritional programs have been discussed in detail in Section 22 on Nutrition.

SCHOOL HEALTH PROGRAMS

Many countries had already started working on the health of children through schools which was an organized set up making it easier for implementing the healthy habits at an early age in a learning environment. Schools are good entry points to begin improving the healthy habits in the homes of these children and thereby in the community at large. Even in India, different states had already been running school health schemes since as early as 1970s. WHO launched its Global School Health Initiative in 1995 with the goal to increase the number of schools that can truly be called *health promoting schools* which can be characterized as a school constantly strengthening its capacity as a healthy setting for living, learning and working. The Government of India launched the school health scheme in 1996–1997, but it was mainly focused on some screening tests and the interest of the administrators gradually began declining. It was then under the National Rural Health Mission (now being transformed into National Health Mission) in 2005 that offered an opportunity to strengthen *school health program*. The Central Board of Secondary Education (CBSE) in India communicated to all schools to carry out a comprehensive school health program, beyond just health checkups. The national curriculum framework in India also recommended that health education should be incorporated as a part of the curriculum (Ministry of Health and Family Welfare, Government of India, 2014).

EMERGING ASPECTS IN DEVELOPING COUNTRIES

The expansion of vaccination programs by way of increasing the number of antigens administered to increasing the coverage is one of the programmatic efforts for child health that is rapidly emerging. The large scale success of polio eradication program is making way for its successor child health program, i.e., global elimination of measles in order to reduce the measles related childhood deaths.

As child health cannot be completely isolated from the health of individuals at other stages of life cycle, it is being advocated that a life cycle approach should be followed for better child health outcomes. Healthy newborns are an outcome of healthy mothers which is affected by the nutrition and health status of the adolescent girls and the avoidance of early pregnancy (Feachem RGA, 1992). In India this acceptance of life cycle approach at the program level was evident when the Child Survival and Safe Motherhood Program was changed to Reproductive and Child Health Program by adding the component of adolescent health in addition to other programmatic changes. Child development, injuries, noncommunicable diseases, birth defects and hemoglobinopathies are some of the other health issues of childhood likely to gain prominence in national health programs of the developing countries in the coming years.

MORE ON THIS TOPIC

Belli PC, Bustreo F, Preker A. Investing in children's health: what are the economic benefits? Bull World Health Organ. 2005;83:777-84.

UNICEF. Convention of rights of the child. From: http://www.unicef.org/crc/. Accessed, December 14, 2014.

Feachem RGA, Phillips MA, Bulatao RA. Introducing adult health. In: Feachem RGA. The Health of Adults in the Developing World. Washington, DC: The World Bank; Oxford University Press; 1992.

Integrated Child Development Services (ICDS) scheme. Ministry of Women and Child Development, Government of India. From: http://wcd.nic.in/icds.htm. Accessed on December 14, 2014.

United Nations. Millenium Development Goals. From: http://www.un.org/millenniumgoals/. Accessed on December 14, 2014.

Reich MR. The politics of agenda setting in international health: child health versus adult health in developing countries. J Int Dev. 1995;7:489-502.

School Health Program. Ministry of Health and Family Welfare, Government of India. From: http://www.mohfw.nic.in/showfile.php?lid=660. Accessed on December 14, 2014.

UNICEF. The State of the World's Children. New York: Oxford University Press, 1983.

World Health Organization. Factsheet on Millenium Development Goals, 2014. From: http://www.who.int/mediacenter/factsheets/fs290/en/. Accessed on December 14, 2014.

Chapter 51.5

Integrated Management of Neonatal and Childhood Illness (IMNCI)

AK Patwari

Child survival, a novel concept to achieve a revolution in child survival and development, was introduced by UNICEF in 1983 within the paradigm of *selective primary health care*. This concept aimed to target high-risk groups with carefully selected cost-effective interventions for under-5 children with a goal to reduce under-5 mortality in third-world countries to half by year 2000. To begin with, the strategy included growth monitoring, oral rehydration therapy, breastfeeding and immunization (GOBI) as specific interventions to achieve the goal. This approach was further expanded to GOBI-FFF (family planning, food supplementation and female education). However, the ultimate goal of reducing under-5 mortality to half by year 2000 seemed distant even though several evidence-based effective interventions like immunization, oral rehydration therapy and use of appropriate antibiotics for treatment of pneumonia were available. In mid-90s, WHO and UNICEF launched the integrated management of childhood illness (IMCI) strategy to improve child survival and reduce deaths from the major causes of under-5 mortality. The strategy has been implemented in more than 75 countries across the world, each country given an opportunity to adapt the guidelines as per local needs. Integrated management of neonatal and childhood illness (IMNCI) is the Indian adapted version of the strategy with a strong neonatal component. The strategy was introduced in India in 2003 to improve the child survival intervention coverage and reach the fourth millennium development goal (MDG 4).

Rationale

Common childhood illnesses like acute respiratory infections, diarrhea, measles, malaria, and malnutrition continue to result in high mortality among children less than 5 years of age. Neonatal mortality contributes to almost 2/3rd of infant deaths and most of these deaths occur during the first week of life. Specifically targeting these common problems and assessing a child for other associated problems provides a holistic approach to manage common childhood illnesses. *Integrated approach* is another effective step because often a young infant or child suffers from more than one illness and common childhood illnesses in this age group have similar presenting symptoms. Moreover, poor access to health-care and delay in referral further compound the problem. Therefore, for early detection and prompt treatment of sickness in under-5 children, there is a need for holistic and integrated approach to childhood illnesses as well as improved access to health-care by community.

Essential Components of IMNCI Strategy

IMNCI strategy includes both preventive and curative interventions that aim to improve case management practices in health facilities, the health system and at home. The strategy includes three main components:
- Improvements in the case-management skills of health staff;
- Improvements in the overall health system; and
- Improvements in family and community health-care practices.

IMNCI CLINICAL GUIDELINES

Integrated management of neonatal and childhood illness clinical guidelines target children less than 5 years old, the age group that bears the highest burden of deaths. It primarily caters to sick under-5 children in outpatient settings (a first-level health facility or OPD of a hospital). The guidelines represent an evidence-based, syndromic approach to case management that includes rational, effective and affordable use of drugs and diagnostic tools. In situations where laboratory support and clinical resources are limited, the syndromic approach is a more realistic and cost-effective way to manage patients. Careful and systematic assessment of common symptoms, using well-selected reliable clinical signs, helps to guide rational and effective actions. An evidence-based syndromic approach is used to determine: (a) health problem(s) the child may have; (b) severity of the child's condition; and (c) actions that can be taken to care for the child (e.g., refer the child immediately, manage with available resources, or manage at home).

Principles of Integrated Care

Depending on a child's age, various clinical signs and symptoms differ in their reliability and diagnostic value. IMNCI clinical guidelines focus on neonates, infants and children up to 5 years of age. However, in view of similarities in the spectrum of illnesses, clinical signs and management protocols, the treatment guidelines have been broadly described under two age categories:
- Sick young infants age up to 2 months (*sick young infant*)
- Sick children age 2 months up to 5 years (*sick child*)

Integrated management of neonatal and childhood illness guidelines are based on the following principles:
- All children under 5 years of age must be examined for conditions which indicate immediate referral.
- Children must be routinely assessed for major symptoms, nutritional and immunization status, feeding problems and other problems.
- Only a limited number of carefully selected clinical signs are used for assessment.
- *Classification* A combination of individual signs is used rather than a *diagnosis*. Classifications are color coded and suggest referral (pink), treatment in health facility (yellow) or management at home (green).
- Guidelines address most common, but not all pediatric problems.
- Management procedures use a limited number of essential drugs.
- Caretakers are actively involved in the treatment of children.
- Counseling of caretakers about home care including feeding, fluids and when to return to health facility is an essential component of IMNCI.

Case management process is summarized in **Flow chart 1** and steps listed in **Box 1**.

Assessment of Sick Young Infant or Child

Sick young infants or sick children are assessed using selected reliable clinical signs and symptoms **(Annexure 1)**. All sick young infants are checked for *very severe disease* and jaundice, feeding problems and malnutrition, immunization status and if they have other problems. They are also assessed for signs of dehydration if have diarrhea. All sick children are checked for *general danger signs*, followed by assessment for main symptoms if they have cough or difficult breathing, diarrhea, fever or ear problems. All sick children are checked for malnutrition, anemia, immunization status, prophylactic vitamin A and iron folic acid supplementation status, and other problems.

Flow chart 1 IMNCI case management process

For all sick children up to 5 years who are brought to a first-level health facility (OPD of a hospital)

Select age appropriate treatment chart

Sick young infant age up to 2 months

Sick child age 2 months up to 5 years

Danger signs:
- Convulsions
- Lethargy/unconsciousness
- Inability to drink/breastfeed
- Vomiting

Possible bacterial infection ← Check everyone →

- Cough or difficult breathing
- Diarrhea
- Fever
- Ear problem

Ask for major symptoms and assess if present

Diarrhea ←

- Malnutrition
- Anemia
- Immunization
- Prophylactic vitamin A status
- Prophylactic IFA Supplementation status

- Feeding problem and malnutrition
- Immunization

Check everyone ←

Assess other problems

Classify illness and identify treatment (use color coded treatment charts)

Pink
Urgent referral

Outpatient health facility:
- Prereferral treatments
- Advise parents
- Refer young infant/child

Pink
Urgent referral

Referral facility:
- Emergency triage and treatment
- Diagnosis
- Treatment
- Monitoring and follow-up

Yellow
Treatment at outpatient health facility

Outpatient health facility:
- Treat local infection
- Give oral drugs
- Advise and teach caretaker
- Follow-up

Give follow-up care when young infant/child returns to clinic and, if necessary, reassess for any new problem

Green
Home management

Home caretaker is counselled how to:
- Give oral drugs
- Treat local infections
- Continue exclusive breastfeeding
- Keep the young infant warm
- When to return immediately
- Follow-up

Classify Illness

The classification tables **(Annexure 1)**, classify the sick young infant or sick child based on the presence of clinical signs. Classification tables are used starting with the *pink* rows, followed by *yellow* and *green* rows. If the sick young infant or sick child has no pink classifications, look at the *yellow* rows. For the classification

tables that have a *green* row, if the young infant does not have any of the signs in the *pink* or *yellow* rows, select the classification in the *green* row. A sick young infant or sick child is classified in one color only under each group of symptoms. If the young infant has signs from more than one row, the most severe (*pink*) classification is selected. However, if the classification table has more than one

BOX 1	Steps of IMNCI case management process

1. Assess the young infant/child
2. Classify the illness
3. Identify treatment
4. Treat the young infant/child
5. Counsel the mother
6. Follow-up care

arm (*possible bacterial infection* or jaundice and diarrhea in a sick young infant, and diarrhea and fever in a sick child), one can choose a classification from each arm. IMNCI classifications are not necessarily specific diagnoses, but they indicate what *action* needs to be taken. *Pink* classification calls for hospital referral or admission in the in-patient section of the hospital, *yellow* for treatment under supervision in the health facility, and *green* means that the child can be sent home with careful advice on when to return.

Identify Treatment

After classifying a sick young infant or sick child the next step is to identify treatment. All the treatments required are listed in the *identify treatment* column of the assess and classify the sick young infant or child chart (**Annexure 1**). If a sick young infant or sick child has more than one classification, treatment required for all the classifications must be identified. Wherever the chart says "Refer URGENTLY to hospital", it pertains to referral to a higher level health facility which could be a health facility with inpatient beds, supplies and expertise to treat a very sick young infant or child. Referral may also mean admission to the inpatient department from the outpatient or casualty of the same facility.

Treatment of Sick Young Infants

Referral All sick young infant with a severe classification (pink) are referred to a hospital as soon as assessment is completed and necessary prereferral treatment is administered. However, if a sick young infant has only severe dehydration and no other severe classification, and IV infusion is available in the outpatient clinic, an attempt should be made first to rehydrate the infant and reassess and reclassify the infant after hydration.

Possible Prereferral Treatments
- First dose of intramuscular or oral antibiotics (gentamicin + ampicillin or ceftriaxone or cefotaxime or oral amoxycillin).
- If infant is convulsing, give diazepam IV or rectally.
- Treatment of severe dehydration according to Plan C of WHO Guidelines for treatment of dehydration.
- Keeping the infant warm on the way to the hospital.
- Prevention of hypoglycemia with breastmilk or sugar water (four level teaspoons of sugar in a 200 mL cup of clean water). If young infant is not able to swallow give expressed breast milk/appropriate animal milk with added sugar/sugar water by nasogastric (NG) tube.
- In sick young infant with diarrhea, give frequent sips of ORS solution on the way to the hospital if he/she can drink orally.

Treatment in Outpatient Clinics
- Treat *some* and *no* dehydration according to Plan B and Plan A respectively, as per WHO Guidelines for treatment of dehydration.
- Treat local bacterial infection with oral antibiotic (amoxicillin) and administer the first dose in the clinic. In addition, the

mother or caretaker should be taught how to give an oral antibiotic at home.
- Teach the mother to apply 0.5% gentian violet twice daily for umbilicus that is red or draining pus and skin pustules. For oral thrush use 0.25% gentian violet twice daily. Show the mother how to wick her child's ear dry. Advise her to dry the ear three times daily.
- Teach correct positioning and attachment for breastfeeding. Teach the mother to manage breast and nipple problems. Counsel about other feeding problems.
- *Advise when to return* To return *immediately* if any of the danger signs (breastfeeding/drinking poorly, becomes sicker, develops a fever or feels cold to touch, fast/difficult breathing, yellow palms and soles if young infant has jaundice, presence of visible blood in stools in young infants with diarrhea)
- *Follow-up visit* For local bacterial infection, jaundice, diarrhea, any feeding problem or oral thrush follow-up after 2 days, and for low weight for age, advise follow-up after 14 days.
- Counsel the mother about her own health.

Treatment of Sick Children

Referral All sick children with a severe classification (*pink*) are referred to a hospital as soon as assessment is completed and necessary pre-referral treatment is administered. If a child has only severe dehydration and no other severe classification, and IV infusion is available in the outpatient clinic, an attempt should be made first to rehydrate the sick child and reassess and re-classify the infant after hydration.

Possible Prereferral Treatments
- For convulsions diazepam IV or rectally. If convulsions continue after 10 min, administer the second dose.
- First dose of appropriate intramuscular antibiotic— chloramphenicol or ampicillin + gentamicin or ceftriaxone (for severe pneumonia or severe disease; very severe febrile disease; severe complicated measles; mastoiditis).
- First dose of quinine (for severe malaria) as per guidelines of National Vectorborne Disease Control Program.
- Vitamin A (persistent diarrhea, measles, severe malnutrition).
- Prevention of hypoglycemia with breastmilk or sugar water.
- Oral antimalarial as per National Malaria Program guidelines.
- Paracetamol for high fever (38.5°C or above) or pain.
- Tetracycline eye ointment (if clouding of the cornea or pus draining from eye).
- Frequent sips of ORS solution on the way to the hospital in sick children with diarrhea hospital if he/she can drink orally.

If a child does not need urgent referral, check to see if the child needs nonurgent referral for further assessment; for example, for a cough that has lasted more than 30 days, or for fever that has lasted 7 days or more. These referrals are not as urgent, and other necessary treatments may be done before transporting for referral.

Treatment in Outpatient Clinic
- *Give the first dose of the antibiotics* Amoxicillin for 5 days for *pneumonia* and *acute ear infection*, ciprofloxacin for 3 days for *dysentery*, and a single dose of doxycycline for *cholera*. For malaria, give choloroquin or artesunate depending upon risk area for *malaria* and rapid blood test or blood smear report.
- Treat *some* and *no* dehydration according to Plan B and Plan A, respectively, as per WHO Guidelines for treatment of dehydration.
- For *persistent diarrhea*, encourage the mother to continue breastfeeding and manage as per WHO guidelines.
- Give iron folic acid for treatment of anemia.

- Use safe home remedies for cough and cold. Breastmilk alone is a good soothing remedy.
- For local infection, teach the mother or caretaker how to treat the infection at home. Instructions may be given about how to treat eye infection with tetracycline eye ointment; dry the ear by wicking to treat ear infection; and treat mouth ulcers with gentian violet.
- All children less than 2 years old and all children classified as *anemia* or *very low weight* need to be assessed for feeding even if they have a normal *Z*-score. Feeding assessment includes questioning the mother or caretaker about: (1) breastfeeding frequency and night feeds; (2) types of complementary foods or fluids, frequency of feeding and whether feeding is active; and (3) feeding patterns during the current illness. The mother or caretaker should be given appropriate advice to help overcome any feeding problems found. One must listen to the mother and compliment her for correct feeding practices; and teach and encourage her to change those practices which need to be changed. Based on assessment of child's usual feeding and feeding during sickness, counsel the mother about feeding the child as per the feeding. recommendations during sickness and health **(Annexure 2)**
- *Advise when to return*: To return *immediately* if the sick child is not able to drink or breastfeed, becomes sicker or develops a fever. If a child with *no pneumonia*: cough or cold has fast/difficult breathing and a child with diarrhea has blood in stools or drinks poorly.
- *Follow-up visits*: Advise the mother to come for follow-up visit after 2 days for *pneumonia*, *dysentery, malaria, fever*—malaria unlikely (if fever persists), *measles* with eye or mouth *complications*; after 5 days for *diarrhea*, if not improving, *persistent diarrhea*, *acute ear infection*, *chronic ear infection, feeding problem*, any other illness if not improving; after 14 days for *anemia* and after 30 Days for very low weight for age.
- Advise the mother when to return for next immunization according to immunization schedule.

Counseling the Mother or Caretaker

Counseling a mother/caretaker is critical not only for successful referral of a severely ill young infant but also for treatment in the outpatients clinic as well as for home care. Good communication skills need to be used from the beginning of the visit particularly while counseling the mother/caretaker for treatment. Good communication skills based on principles of APAC (Ask and Listen, Praise, Advise and Check) are helpful for effective counseling. *Ask and listen* to find out the infant's problems and what the mother is already doing for the infant; *praise* the mother for what she has done well; *advise* her how to care for her infant at home; and *check* the mother's understanding before she leaves.

A child who is seen at the clinic needs to continue treatment, feeding and fluids at home. The child's mother or caretaker also needs to recognize when the child is not improving, or is becoming sicker. The success of home treatment depends on how well the mother or caretaker knows how to give treatment, understands its importance and knows when to return to a health-care provider. Some advice is simple; other advice requires teaching the mother or caretaker how to do a task. When a mother is taught how to treat her child at home, three basic teaching steps need to be used: give information; show an example; let her practice.

FACILITY BASED IMNCI

Introduction of IMCI/IMNCI strategy clearly offers several benefits to children in areas where it is implemented. Experience from across the world has demonstrated improvement in health worker performance, better quality of care, increased use of health services and rational drug use at costs that are lower or similar to investments in routine child health services. However, IMNCI approach has been perceived as a strategy with limited scope because of its relevance to peripheral health facilities commonly manned by health workers. Over the years implementation of IMNCI strategy at primary care level was not linked to standard clinical medicine practiced in the hospitals. Moreover, for the management of very sick young infants or children the guidelines stop short at referral of *pink* classifications to a hospital. Uncertainty about continuum of care to the next level as per IMNCI guidelines has been a great influence on health workers' confidence while handling sick children at a first-level health facility in the field.

Government of India has developed *facility-based IMNCI (F-IMNCI)* guidelines for care of children under the age 5 years after they are referred to a hospital with *"pink"* classification/s, or delivered in the hospital itself or directly brought to the hospital. These guidelines are directed at small hospitals where basic laboratory facilities and inexpensive essential drugs are available. Concept of F-IMNCI recognizes the importance of evidence based IMNCI guidelines as practiced by the health-care providers at first level facilities and describes a sequential process for managing sick young infants and children as soon as they arrive in hospital. It also introduces a change in IMNCI approach from *classification* of illness to making a clinical *diagnosis*. F-IMNCI guidelines are consistent and support IMNCI training materials for outpatient management of young infants or sick children. These evidence based guidelines also complements standard comprehensive pediatric textbooks.

F-IMNCI guidelines provide appropriate inpatient management of the major causes of neonatal and childhood mortality such as asphyxia, sepsis, meningitis, diarrhea, neonatal jaundice, tetanus neonatorum and low birthweight in neonates; and pneumonia, pleural effusion or empyema, asthma, stridor, diarrhea, malaria, dengue fever, meningitis, typhoid fever, severe anemia and severe acute malnutrition in children up to the age of 5 years. The treatment guidelines include emergency triage and treatment (ETAT), care at birth, neonatal transport, management in a neonatal care unit, and management in postnatal and pediatric ward. F-IMNCI also trains health care providers in oxygen administration, use of inhalers or spacers, starting intraosseous line, pulse oximetry and diagnostic procedures. A continuum of care to sick children in a hospital as per F-IMNCI guidelines brings credence to IMNCI case management guidelines for managing a huge population of under-5 children in areas with limited access to hospitals.

MORE ON THIS TOPIC

Gove S. Integrated management of childhood illness by outpatient health workers: technical basis and overview. The WHO Working Group on Guidelines for Integrated Management of the Sick Child. Bull World Health Organ.1997;75 Suppl 1:7-24.

Ministry of Health and Family Welfare. Facility Based IMNCI (F-IMNCI). Participants Manual. New Delhi: Govt. of India; 2009.

Ministry of Health and Family Welfare. Integrated Management of Neonatal and Childhood Illness: Training Modules for Physicians. New Delhi: Govt. of India; 2003.

World Health Organization Management of the Child with a Serious Infection or Severe Malnutrition: Guidelines for care at the first-referral level in developing countries. Geneva: WHO; 2000.

World Health Organization. Technical updates of the guidelines on the IMCI: Evidence and recommendations for further adaptations. Geneva: WHO; 2005.

Annexure 1

ASSESS AND CLASSIFY THE SICK YOUNG INFANT AGE UPTO 2 MONTHS

ASSESS

Ask the mother what the young infant's problems are

- Determine if this is an initial or follow-up visit for this problem.
  - if follow-up visit, use the follow-up instructions on the bottom of this chart.
  - if initial visit, assess the young infant as follows

CLASSIFY

USE ALL BOXES THAT MATCH INFANT'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

IDENTIFY TREATMENT

A child with a pink classification needs URGENT attention, complete the assessment and prereferral treatment immediately so referral is not delayed

---

CHECK FOR POSSIBLE BACTERIAL INFECTION/JAUNDICE

		SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent prereferral treatments are in bold print.)
ASK:	**LOOK, LISTEN, FEEL:**			
• Has the infant had convulsions?	• Count the breaths in one minute. Repeat the count if elevated.	} YOUNG INFANT MUST BE CALM		
	• Look for severe chest indrawing.			
	• Look for nasal flaring.			
	• Look and listen for grunting.			
	• Look and feel for bulging fontanelle.			
	• Look for pus draining from the ear.			
	• Look at the umbilicus. Is it red or draining pus?			
	• Look for skin pustules. Are there 10 or more skin pustules or a big boil?			
	• Measure axillary temperature (if not possible, feel for fever or low body temperature).			
	• See if the young infant is lethargic or unconscious.			
	• Look at the young infant's movements. Are they less than normal?			
	• Look for jaundice?			
	• Are the palms and soles yellow?			

CLASSIFY ALL YOUNG INFANTS

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT
• Convulsions or • Fast breathing (60 breaths per minute or more) or • Severe chest indrawing or • Nasal flaring or • Grunting or • Bulging fontanelle or • 10 or more skin pustules or a big boil or • If axillary temperature 37.5°C or above (or feels hot to touch) or temperature less than 35.5°C (or feels cold to touch) or • Lethargic or unconscious or • Less than normal movements.	**POSSIBLE SERIOUS BACTERIAL INFECTION**	➢ **Give first dose of intramuscular ampicillin and gentamicin.** ➢ **Treat to prevent low blood sugar.** ➢ **Warm the young infant by skin to skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral.** ➢ **Advise mother how to keep the young infant warm on the way to the hospital.** ➢ **Refer URGENTLY to hospital"**
• Umbilicus red or draining pus or • Pus discharge from ear or • < 10 skin pustules.	**LOCAL BACTERIAL INFECTION**	➢ **Give oral amoxicillin for 5 days.** ➢ Teach mother to treat local infections at home. ➢ Follow–up in 2 days.

AND IF THE INFANT HAS JAUNDICE

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT
• Palms and soles yellow or • Age < 24 hours or • Age 14 days or more	**SEVERE JAUNDICE**	➢ **Treat to prevent low blood sugar.** ➢ **Warm the young infant by skin to skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral.** ➢ **Advise mother how to keep the young infant warm on the way to the hospital.** ➢ **Refer URGENTLY to hospital.**
• Palms and soles not yellow	**JAUNDICE**	➢ Advise mother to give home care for the young infant. ➢ Advise mother when to return immediately. ➢ Follow–up in 2 days.

AND IF THE TEMP. IS BETWEEN 35.5–36.4°C

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT
• Temperature between 35.5–36.4°C	**LOW BODY TEMPERATURE**	➢ Warm the young infant using skin to skin contact for one hour and REASSESS. If no improvement, refer ➢ Treat to prevent low blood sugar.

"If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Young Infant and Counsel the Mother.**

Contd...

THEN ASK:
Does the young infant have diarrhea?*

IF YES, ASK:
- For how long?
- Is there blood in the stool?

LOOK AND FEEL:
- Look at the young infant's general condition. Is the infant:
  - Lethargic or unconscious?
  - Restless and irritable?
- Look for sunken eyes.
- Pinch the skin of the abdomen. Does it go back:
  - Very slowly (longer than 2 seconds)?
  - Slowly?

CLASSIFY DIARRHEA

FOR DEHYDRATION

Two of the following signs:
- Lethargic or unconscious
- Sunken eyes
- Skin pinch goes back very slowly

SEVERE DEHYDRATION

➤ Give first dose of intramuscular ampicillin and gentamicin.
➤ If infant also has low weight or another severe classification:
- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.
- Advise mother to continue breastfeeding.
- Advise mother how to keep the young infant warm on the way to the hospital.

OR

➤ If infant does not have low weight or any other severe classification:
- Give fluid for severe dehydration (Plan C) and then refer to hospital after rehydration.

Two of the following signs:
- Restless, irritable
- Sunken eyes
- Skin pinch goes back slowly

SOME DEHYDRATION

➤ If infant also has low weight or another severe classification:
- Give first dose of intramuscular ampicillin and gentamicin
- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.
- Advise mother to continue breastfeeding.
- Advise mother how to keep the young infant warm on the way to the hospital.
➤ If infant does not have low weight or another severe classification:
- Give fluids for some dehydration (Plan B).
- Advise mother when to return immediately.
- Follow-up in 2 days

- Not enough signs to classify as some or severe dehydration

NO DEHYDRATION

➤ Give fluids to treat diarrhea at home (Plan A).
➤ Advise mother when to return immediately.
➤ Follow-up in 5 days if not improving.

AND IF DIARRHEA 14 DAYS OR MORE

- Diarrhea lasting 14 days or more

SEVERE PERSISTENT DIARRHEA

➤ Give first dose of intramuscular ampicillin and gentamicin if the young infant has low weight, dehydration or another severe classification.
➤ Treat to prevent low blood sugar.
➤ Advise how to keep infant warm on the way to the hospital."
➤ Refer to hospital."

AND IF BLOOD IN STOOL

- Blood in the stool

SEVERE DYSENTERY

➤ Give first dose of intramuscular ampicillin and gentamicin if the young infant has low weight, dehydration or another severe classification.
➤ Treat to prevent low blood sugar.
➤ Advise how to keep infant warm on the way to the hospital.
➤ Refer to hospital."

* What is diarrhea in a young infant?
If the stools have changed from usual pattern and are many and watery (more water than fecal matter). The normally frequent or loose stools of a breastfed baby are not diarrhea.

 # If referral is not possible, see the section Where Referral is Not Possible in the module Treat the Young Infant and Counsel the Mother.

Contd...

Contd...

THEN CHECK FOR FEEDING PROBLEM AND MALNUTRITION

ASK:

- Is there any difficulty feeding?
- Is the infant breastfed? If yes, how many times in 24 hours?
- Does the infant usually receive any other foods or drinks?
  If yes, how often?
- What do you use to feed the infant?

IF AN INFANT:

- Does the mother have pain while breastfeeding?

LOOK, FEEL:

- Determine weight for age.

Has any difficulty feeding, or
Is breastfeeding less than 8 times in 24 hours, or
Is taking any other foods or drinks, or
Is low weight for age,
AND
Has no indications to refer urgently to hospital:

ASSESS BREASTFEEDING:

- Has the infant breastfed in the previous hour?

  If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe the breastfeed for 4 minutes.
  (If the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again)

  - Is the infant able to attach?
    no attachment at all   not well attached   good attachment

    > **TO CHECK ATTACHMENT, LOOK FOR:**
    > - Chin touching breast
    > - Mouth wide open
    > - Lower lip turned outward
    > - More areola visible above than below the mouth
    > *(All of these signs should be present if the attachment is good)*

  - Is the infant suckling effectively (that is, slow deep sucks, sometimes pausing)?
    not suckling at all   not suckling effectively   suckling effectively
    Clear a blocked nose if it interferes with breastfeeding.

  - Look for ulcers or white patches in the mouth (thrush).

  If yes, look and feel for:
  - Flat or inverted nipples, or sore nipples
  - Engorged breasts or breast abscess

CLASSIFY FEEDING

Signs	Classify as	Treatment
• Not able to feed or • No attachment at all or • Not suckling at all or • Severely underweight (< -3 SD)	**NOT ABLE TO FEED — POSSIBLE SERIOUS BACTERIAL INFECTION OR SEVERE MALNUTRITION**	➢ **Give first dose of intramuscular ampicillin and gentamicin.** ➢ **Treat to prevent low blood sugar.** ➢ **Warm the young infant by skin to skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral.** ➢ **Advise mother how to keep the young infant warm on the way to the hospital.** ➢ **Refer URGENTLY to hospital"**
• Not well attached to breast or • Not suckling effectively or • Less than 8 breastfeeds in 24 hours or • Receives other foods or drinks or • Thrush (ulcers or white patches in mouth) or • Moderately underweight (< -2 to -3 SD) or • Breast or nipple problems	**FEEDING PROBLEM OR LOW WEIGHT FOR AGE**	➢ If not well attached or not suckling effectively, teach correct positioning and attachment. ➢ If breastfeeding less than 8 times in 24 hours, advise to increase frequency of feeding. ➢ If receiving other foods or drinks, counsel mother about breastfeeding more, reducing other foods or drinks, and using a cup and spoon. - If not breastfeeding at all, advise mother about giving locally appropriate animal milk and teach the mother to feed with a cup and spoon. ➢ If thrush, teach the mother to treat thrush at home. ➢ If low weight for age, teach the mother how to keep the young infant with low weight warm at home. ➢ If breast or nipple problem, teach the mother to treat breast or nipple problems. ➢ Advise mother to give home care for the young infant. ➢ Advise mother when to return immediately. ➢ Follow-up any feeding problem or thrush in 2 days. ➢ Follow-up low weight for age in 14 days.
• Not low weight for age (≥ -2SD) and no other signs of inadequate feeding	**NO FEEDING PROBLEM**	➢ Advise mother to give home care for the young infant. ➢ Advise mother when to return immediately. ➢ Praise the mother for feeding the infant well.

If referral is not possible, see the section Where **Referral Is Not Possible** in the module **Treat the Young Infant and Counsel the Mother.**

THEN CHECK THE YOUNG INFANT'S IMMUNIZATION STATUS

IMMUNIZATION SCHEDULE*

AGE	VACCINE	
Birth	BCG	OPV 0
6 weeks	DPT I	OPV I HEP-B I

* **Hepatitis B to be given wherever included in the immunization schedule**

ASSESS OTHER PROBLEMS

ASSESS AND CLASSIFY THE SICK CHILD CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS   CLASSIFY   IDENTIFY TREATMENT

ASSESS

ASK THE MOTHER WHAT THE CHILD'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
  – if follow-up visit, use the follow-up instructions on *TREAT THE CHILD* chart.
  – if initial visit, assess the child as follows:

CHECK FOR GENERAL DANGER SIGNS

ASK:

- Is the child able to drink or breastfeed?
- Does the child vomit everything?
- Has the child had convulsions?

LOOK

- See if the child is lethargic or unconscious.

A child with any general danger sign needs URGENT attention; complete the assessment and any prereferral treatment immediately so referral is not delayed.

THEN ASK ABOUT MAIN SYMPTOMS:
Does the child have cough or difficult breathing?

IF YES, ASK: **LOOK, LISTEN:**

- For how long?
- Count the breaths in one minute.
- Look for chest indrawing.
- Look and listen for stridor.

CHILD MUST BE CALM

CLASSIFY COUGH OR DIFFICULT BREATHING

If the child is:	Fast breathing is:
2 months up to 12 months	50 breaths per minute or more
12 months up to 5 years	40 breaths per minute or more

USE ALL BOXES THAT MATCH THE CHILD'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent prereferral treatments are in bold print)
• Any general danger sign or • Chest indrawing or • Stridor in calm child	**SEVERE PNEUMONIA OR VERY SEVERE DISEASE**	➤ **Give first dose of injectable chloramphenicol (if not possible give oral amoxycillin).** ➤ **Refer URGENTLY to hospital#**
• Fast breathing	**PNEUMONIA**	➤ **Give amoxycillin for 5 days.** ➤ Soothe the throat and relieve the cough with a safe remedy if child is 6 months or older. ➤ Advise mother when to return immediately. ➤ Follow-up in 2 days.
No signs of pneumonia or very severe disease	**NO PNEUMONIA: COUGH OR COLD**	➤ If coughing more than 30 days, refer for assessment. ➤ Soothe the throat and relieve the cough with a safe home remedy if child is 6 months or older. ➤ Advise mother when to return immediately. ➤ Follow-up in 5 days if not improving.

If referral is not possible, see the section **Where Referral is Not Possible** in the module **Treat the Child.**

Does the child have diarrhea?

IF YES, ASK:

- For how long?
- Is there blood in the stool?

LOOK AND FEEL:

- Look at the child's general condition. Is the child:
  - Lethargic or unconscious?
  - Restless and irritable?
- Look for sunken eyes.
- Offer the child fluid. Is the child:
  - Not able to drink or drinking poorly?
  - Drinking eagerly, thirsty?
- Pinch the skin of the abdomen. Does it go back:
  - Very slowly (longer than 2 seconds)?
  - Slowly?

CLASSIFY DIARRHEA

FOR DEHYDRATION

Signs	Classify as	Treatment
Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly	**SEVERE DEHYDRATION**	➤ If child has no other severe classification: - Give fluid for severe dehydration (Plan C). ➤ *If child also has another severe classification:* **Refer URGENTLY to hospital# with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding.** ➤ *If child is 2 years or older and there is cholera in your area, give doxycycline for cholera.*
Two of the following signs: • Restless, irritable. • Sunken eyes. • Drinks eagerly, thirsty • Skin pinch goes back slowly	**SOME DEHYDRATION**	➤ Give fluid, zinc supplements and food for some dehydration (Plan B). ➤ *If child also has a severe classification:* **Refer URGENTLY to hospital# with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding.** ➤ Advise mother when to return immediately. ➤ Follow-up in 5 days if not improving.
• Not enough signs to classify as some or severe dehydration	**NO DEHYDRATION**	➤ Give fluid, zinc supplements and food to treat diarrhea at home (Plan A). ➤ Advise mother when to return immediately. ➤ Follow-up in 5 days if not improving.

AND IF DIARRHEA 14 DAYS OR MORE

Signs	Classify as	Treatment
• Dehydration present	**SEVERE PERSISTENT DIARRHEA**	➤ *Treat dehydration before referral unless the child has another severe classification.* ➤ *Refer to hospital.#*
• No dehydration	**PERSISTENT DIARRHEA**	➤ Advise the mother on feeding a child who has PERSISTENT DIARRHEA. ➤ *Give single dose of vitamin A.* ➤ Give zinc supplements daily for 14 days. ➤ Follow-up in 5 days.

AND IF BLOOD IN STOOL

Signs	Classify as	Treatment
• Blood in the stool	**DYSENTERY**	➤ *Treat for 3 days with ciprofloxacin.* **Treat dehydration** ➤ Give zinc supplements for 14 days ➤ Follow-up in 2 days.

If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child.**

Does the child have fever?
(by history or feels hot or temperature 37.5°C* or above)

IF YES:
Decide Malaria Risk: High Low

THEN ASK:

LOOK AND FEEL:

- Fever for how long?
- If more than 7 days, has fever been present every day?
- Has the child had measles within the last 3 months?

- Look or feel for stiff neck.
- Look and feel for bulging fontanelle.
- Look for runny nose.

Look for signs of MEASLES

- Generalized rash and
- One of these: cough, runny nose, or red eyes.

If the child has measles now or within the last 3 months:

- Look for mouth ulcers. Are they deep and extensive?
- Look for pus draining from the eye.
- Look for clouding of the cornea.

CLASSIFY FEVER

High Malaria Risk

HIGH MALARIA RISK

Signs	Classify as	Treatment
• Any general danger sign or • Stiff neck or • Bulging fontanelle	**VERY SEVERE FEBRILE DISEASE**	➤ Give first dose of IM quinine after making a smear/RDT ➤ Give first dose of IV or IM chloramphenicol (If not possible, give oral amoxycillin). ➤ Treat the child to prevent low blood sugar. ➤ Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above). ➤ Refer URGENTLY to hospital#.
• Fever (by history or feels hot or temperature >37.5°C or above)	**MALARIA**	➤ Give oral antimalarials for HIGH malaria risk area after making a smear/RDT ➤ Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above) ➤ Advise mother when to return immediately. ➤ Follow-up in 2 days. ➤ If fever is present every day for more than 7 days, refer for assessment.

Low Malaria Risk

LOW MALARIA RISK

Signs	Classify as	Treatment
• Any general danger sign or • Stiff neck or • Bulging fontanelle.	**VERY SEVERE FEBRILE DISEASE**	➤ Give first dose of IM quinine after making a smear. ➤ Give first dose of IV or IM chloramphenicol (If not possible, give oral amoxycillin). ➤ Treat the child to prevent low blood sugar. ➤ Give one dose of paracetamol in clinic for high fever (temp 38.5°C or above). ➤ Refer URGENTLY to hospital#.
• NO runny nose and NO measles and NO other cause of fever	**MALARIA**	➤ Give oral antimalarials for LOW malaria risk area after making a smear ➤ Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above). ➤ Advise mother when to return immediately. ➤ Follow-up in 2 days. ➤ If fever is present every day for more than 7 days, refer for assessment.
• Runny nose PRESENT or • Measles PRESENT or • Other cause of fever PRESENT**	**FEVER— MALARIA UNLIKELY**	➤ Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above). ➤ Advise mother when to return immediately. ➤ Follow-up in 2 days if fever persists ➤ If fever is present every day for more than 7 days, refer for assessment.

If MEASLES Now or within last 3 months, Classify

Signs	Classify as	Treatment
• Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers	**SEVERE COMPLICATED MEASLES***	➤ Give first dose of Vitamin A. ➤ Give first dose of injectable chloramphenicol (If not possible give oral amoxycillin). ➤ If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment. ➤ Refer URGENTLY to hospital#
• Pus draining from the eye or • Mouth ulcers	***MEASLES WITH EYE OR MOUTH COMPLICATIONS***	➤ Give first dose of Vitamin A. ➤ If pus draining from the eye, treat eye infection with tetracycline eye ointment. ➤ If mouth ulcers, treat with gentian violet. ➤ Follow-up in 2 days.
• Measles now or within the last 3 months.	**MEASLES**	➤ Give first dose of Vitamin A

* This cutoff is for axillary temperatures; rectal temperature cutoff is approximately 0.5°C higher.
** Other causes of fever include cough or cold, pneumonia, diarrhea, dysentery and skin infections.
*** Other important complications of measles—pneumonia, stridor, diarrhea, ear infection, and malnutrition—are classified in other tables.

If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child.**

Does the child have an ear problem?

IF YES, ASK:
- Is there ear pain?
- Is there ear discharge? If yes, for how long?

LOOK AND FEEL:
- Look for pus draining from the ear.
- Feel for tender swelling behind the ear.

Classify
EAR PROBLEM

Signs	Classify	Treatment
• Tender swelling behind the ear	**MASTOIDITIS**	➤ **Give first dose of injectable chloramphenicol (If not possible give oral amoxycillin).** ➤ **Give first dose of paracetamol for pain.** ➤ **Refer URGENTLY to hospital#.**
• Pus is seen draining from the ear and discharge is reported for less than 14 days, or • Ear pain.	**ACUTE EAR INFECTION**	➤ **Give amoxycillin for 5 days.** ➤ Give paracetamol for pain. ➤ Dry the ear by wicking. ➤ Follow-up in 5 days.
• Pus is seen draining from the ear and discharge is reported for 14 days or more.	**CHRONIC EAR INFECTION**	➤ Dry the ear by wicking. ➤ Topical ciprofloxacin ear drops for 2 weeks. ➤ Follow-up in 5 days.
• No ear pain and No pus seen draining from the ear.	**NO EAR INFECTION**	No additional treatment.

If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child.**

THEN CHECK FOR MALNUTRITION

LOOK AND FEEL:
- Look for visible severe wasting.
- Look for edema of both feet.
- Determine weight for age.

Classify **NUTRITIONAL STATUS**

Signs	Classify	Treatment
• Visible severe wasting or • Edema of both feet.	**SEVERE MALNUTRITION**	➤ *Give single dose of Vitamin A.* ➤ *Prevent low blood sugar.* ➤ *Refer URGENTLY to hospital#* ➤ *While referral is being organized, warm the child.* ➤ *Keep the child warm on the way to hospital.*
• Severely underweight (<-3 SD)	**VERY LOW WEIGHT**	➤ Assess and counsel for feeding - if feeding problem, follow-up in 5 days ➤ Advise mother when to return immediately ➤ Follow-up in 30 days.
• Not severely underweight (≥-3 SD)	**NOT VERY LOW WEIGHT**	➤ If child is less than 2 years old, assess the child's feeding and counsel the mother on feeding according to the FOOD box on the COUNSEL THE MOTHER chart. - If feeding problem, follow-up in 5 days. ➤ Advise mother when to return immediately.

THEN CHECK FOR ANEMIA

LOOK
- Look for palmar pallor. Is it:
Severe palmar pallor?
Some palmar pallor?

Classify **ANEMIA**

Signs	Classify	Treatment
• Severe palmar pallor	**SEVERE ANEMIA**	➤ Refer URGENTLY to hospital#.
• Some palmar pallor	**ANEMIA**	➤ Give iron folic acid therapy for 14 days. ➤ Assess the child's feeding and counsel the mother on feeding according to the FOOD box on the COUNSEL THE MOTHER chart. - If feeding problem, follow-up in 5 days. ➤ Advise mother when to return immediately. ➤ Follow-up in 14 days.
• No palmar pallor	**NO ANEMIA**	➤ Give prophylactic iron folic acid if child 6 months or older.

THEN CHECK THE CHILD'S IMMUNIZATION*, PROPHYLACTIC VITAMIN A AND IRON-FOLIC ACID SUPPLEMENTATION STATUS

IMMUNIZATION SCHEDULE:

AGE	VACCINE
Birth	BCG + OPV-0
6 weeks	DPT-1 + OPV-1(+ Hep B-1**)
10 weeks	DPT-2 + OPV-2(+ Hep B-2**)
14 weeks	DPT-3 + OPV-3(+ Hep B-3**)
9 months	Measles
16–18 months	DPT Booster + OPV
60 months	DT

PROPHYLACTIC VITAMIN A
Give a single dose of vitamin A:
100,000 IU at 9 months with measles immunization
200,000 IU at 16–18 months with DPT Booster
200,000 IU at 24 months, 30 months, 36 months,
42 months, 48 months, 54 months and 60 months

PROPHYLACTIC IFA
Give 20 mg elemental iron + 100 µg folic acid (one tablet of Pediatric IFA or IFA syrup/IFA drops) for a total of 100 days in a year after the child has recovered from acute illness **if:**
➤ The child is 6 months of age or older, and
➤ Has not received Pediatric IFA Tablet/syrup/drops for 100 days in last one year.

* A child who needs to be immunized should be advised to go for immunization the day vaccines are available at AW/SC/PHC
** Hepatitis B to be given wherever included in the immunization schedule

ASSESS OTHER PROBLEMS

MAKE SURE CHILD WITH ANY GENERAL DANGER SIGN IS REFERRED after first dose of an appropriate antibiotic and other urgent treatments.
Exception: Rehydration of the child according to Plan C may resolve danger signs so that referral is no longer needed.

If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child.**

Annexure 2

COUNSEL THE MOTHER

Feeding Recommendations During Sickness and Health

Up to 6 Months of Age	6 Months up to 12 Months	12 Months up to 2 Years	2 Years and Older
• Breastfeed as often as the child wants, day and night, at least 8 times in 24 hours. • Do not give any other foods or fluids not even water.	• Breastfeed as often as the child wants. • Give at least one katori serving* at a time of: - Mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk OR - Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR - Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR - Mashed boiled/fried potatoes - Offer banana/biscuit/cheeko/mango/papaya	• Breastfeed as often as the child wants. • Offer food from the family pot. • Give at least 1½ katori serving* at a time of: - Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR - Mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk OR - Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR - Mashed boiled/fried potatoes - Offer banana/biscuit/cheeko/mango/papaya	• Give family foods at 3 meals each day. • Also, twice daily, give nutritious food between meals, such as: banana/biscuit/cheeko/mango/papaya as snacks.
Remember: • Continue breastfeeding if the child is sick.	*3 times per day if breastfed; 5 times per day if not breastfed. **Remember:** • Keep the child in your lap and feed with your own hands. • Wash your own and child's hands with soap and water every time before feeding.	* 5 times per day. **Remember:** • Sit by the side of child and help him to finish the serving. • Wash your child's hands with soap and water every time before feeding.	**Remember:** • Ensure that the child finishes the serving. • Teach your child wash his hands with soap and water every time before feeding.

Feeding Recommendations For a Child who Has PERSISTENT DIARRHEA

• If still breastfeeding, give more frequent, longer breastfeeds, day and night.
• If taking other milk:
  - Replace with increased breastfeeding OR
  - Replace with fermented milk products, such as yoghurt OR
  - Replace half the milk with nutrient-rich semisolid food.
  - Add cereals to milk (Rice, Wheat, Semolina).

• For other foods, follow feeding recommendations for the child's age.

LABORATORY VALUES AND DRUG DOSES

Section Editor *Pooja Dewan*

Annexure A
Laboratory Reference Values
Nidhi Bedi, Pooja Dewan

THE NORMAL RANGE

Results of a laboratory test can be interpreted in terms of being normal or abnormal, and negative or positive only on the basis of already known *normal or reference values.* Normal values refer to those measurements which are usually central and around which most of the values lie in healthy individuals.

Almost all normal laboratory values are represented and expressed in a *reference range* and rarely in terms of a single measurement. For example, a large group of healthy children in the age group of 6–12 years may have an average hemoglobin level of 14 g/dL with the individual values ranging from 11.5 g/dL to 15.5 g/dL. In this case, the normal hemoglobin values in 6–12 years old are said to range between 11.5 g/dL and 15.5 g/dL, and not simply 14 g/dL. The normal or reference range is an integral part of all laboratory values because of considerable magnitude of inter-individual variability in the normal population. Variations in normal subjects occur due to a host of reasons, other than age and sex, which may include biological, genetic, environmental and chance factors apart from the interobserver and laboratory variability. In addition, the analytic method used in the laboratory is a major factor affecting the value obtained. All these sources are instrumental in creating a rather wide range of values that may be referred to for classifying an individual as having a normal or abnormal laboratory test.

The central values are measured in terms of mean, median and mode. Fortunately, these three measures generally coincide in most of the laboratory measurements in healthy individuals. The normal deviation around the mean is termed as standard deviation. In a typical Gaussian (bell shaped) distribution curve, 95% of the normal values lie between ± 2 SD around the mean. However, certain laboratory values in normal individuals do not follow the Gaussian curve, making it difficult to assume all values within mean 2 SD as being normal. In such situation, the normal values are expressed in terms of a range covering 95% of values from a set of values found in a healthy population, excluding 2.5% each of the lowermost and uppermost values.

Most of the laboratory tests do not have any absolute or magic cut-off point for labeling their results as being normal and abnormal. For example, if normal range of values of serum urea nitrogen is 5–18 mg/dL in children, then 17 mg/dL carries an importance equivalent to a value of 19 mg/dL. Both these values are then termed *borderline*. Such borderline values can be present in healthy as well as sick subjects and should be interpreted cautiously.

UNITS OF MEASUREMENT

Laboratory estimates are usually expressed as conventional or traditional units. However, it may be appropriate to know the standard units referred to as the SI units. The International System of Units (abbreviated SI from French: *Le Système international d'unités*) is well accepted worldwide as a standard and modern form of metric measurement. For most parameters, the SI units are moles per liter, wherein mass is measured in moles and volume as liters. Concentration in moles is the ratio of the weight in grams and the molecular weight.

To convert a value expressed in conventional units to a SI unit, we need to multiply by the conversion factor. For example, albumin 3 g/dL × 10 = 30 g/L. To convert from SI units to conventional units, we will need to divide the value by a conversion factor. For example,, albumin 30 g/L = 30 ÷ 10 g/dL = 3 g/dL.

COMMON ABBREVIATIONS

Most of the commonly used units are written in an abbreviated from. A list of such units is given below in **Table 1**. Prefixes are used along with the units of length, capacity and mass **(Table 2)**.

Table 1 Abbreviations for common units

Measure	Unit name	Abbreviation
Weight	gram	g
Length	meter	m
Capacity	liter	L
Pressure	millimeter of mercury	mm Hg
Enzyme activity	International unit	U
Volume	cubic millimeter	mm^3
Osmolality	mole	mol
Equivalent weight	milliequivalent	mEq

Table 2 Prefixes used for decimal factors

Prefix	Symbol	Factor
Mega	M	10^6
kilo	k	10^3
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
micro	u	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}

HEMATOLOGICAL VALUES

Parameter	Traditional or conventional units	Standard units (multiplication factor)
Blood volume	*mL/kg*	*mL/kg (1.0)*
At birth	61–100	61–100
Infants	73–78	73–78
1–3 years	74–82	74–82
4–6 years	80–86	80–86
7–18 years	83–90	83–90
Adults	68–88	68–88
Erythrocyte sedimentation rate (ESR): Westergren Method	*mm/h*	*mm/h (1.0)*
Neonate	0–4	0–4
Child	4–20	4–20
Adult males	0–10	0–10
Adult females	0–20	0–20
Hematocrit	*%*	*% (1.0)*
Birth	55 (45–65)	55 (45–65)
1 week	54 (43–66)	54 (43–66)
1–2 weeks	50 (42–66)	50 (42–66)
6 months–6 years	38 (33–42)	38 (33–42)
> 6 year males	46 (42–52)	46 (42–52)
> 6 year females	42 (37–47)	42 (37–47)
Hemoglobin (Total) (Hgb)	*g/dL*	*mmol/L (0.6206)*
Birth	17 (14–20)	11.25 (8.68–12.41)
1 week	17 (13–21)	11.25 (8.06–13.06)
1–2 weeks	16.5 (13–20)	10.24 (8.06–12.41)
6 months–6 years	12 (10.5–14)	7.45 (6.15–8.68)
6–12 years	14 (11.5–15.5)	8.68 (7.14–9.62)
Adolescent males	16 (14–18)	9.93 (8.68–11.17)
Adolescent females	14 (12–16)	8.68 (7.45–9.93)
Hemoglobin A	≥ 95% of total Hgb	≥ 95% of total Hgb
Hemoglobin A_2	1.5–3.5% of total Hgb	1.5–3.5% of total Hgb
Hemoglobin A_{1c} (Glycated Hgb)	4.5–6.1% of total Hgb	4.5–6.1% of total Hgb
Hemoglobin fetal (Hgb F)	*% of total Hgb*	*% of total Hgb*
Neonate	60–90	60–90
Infant	2–59	2–59
Child	< 2	< 2
Adolescent	< 2	< 2
Adult	< 2	< 2
Methemoglobin	0–1.3% of total Hgb	0–1.3% of total Hgb

Contd...

Mean corpuscular hemoglobin (MCH)	*pg*	*pg*
Birth	32–40	32–40
1 week	32–40	32–40
1–2 weeks	32–40	32–40
6 months–6 years	24–30	24–30
> 6-year males	27–32	27–32
> 6-year females	27–32	27–32
Mean corpuscular hemoglobin concentration (MCHC)	*g/dL*	*g/L (10)*
Birth	34–36	340–360
1 week	34–36	340–360
1–2 weeks	34–36	340–360
6 months–6 years	30–36	300–360
> 6-year males	30–35	300–350
> 6-year females	30–35	300–350
Mean corpuscular volume (MCV)	*fL*	*fL*
Birth	94–118	94–118
1 week	88–104	88–104
1–2 weeks	86–106	86–106
6 months–6 years	76–88	76–88
> 6-year males	76–98	76–98
> 6-year females	76–96	76–96
Plasma volume	*mL/kg*	*mL/kg (1.0)*
At birth	33.5–49.5	33.5–49.5
Males	25–43	25–43
Females	28–45	28–45
Platelet count	*X 10^3/mm^3*	*X 10^9/L*
Birth	100–300	100–300
1 week–adults	150–450	150–450
Red blood cell count	*X 10^6 cells/mm^3*	*X 10^{12} cells/L(1.0)*
Birth	3.7–6.5	3.7–6.5
2 weeks	3.9–5.9	3.9–5.9
2 months	3.1–4.3	3.1–4.3
6 months	3.8–4.9	3.8–4.9
1 year	3.9–5.1	3.9–5.1
2–6 years	3.9–5.0	3.9–5.0
6–12 years	3.9–5.2	3.9–5.2
Reticulocyte count	*%*	*% (1.0)*
Birth	5 (3–7)	5 (3–7)
2 weeks	2 (0–4)	2 (0–4)
months–6 years	1 (0–2)	1 (0–2)
6–12 years	0–2	0–2
White blood cell count	*cells/mm^3*	*X 10^9 cells/L (10^6)*
Birth	18000 (9000–30000)	18 (9–30)
1 week	12000 (6000–22000)	12 (6–22)
2 weeks	12000 (5000–21000)	12 (5–21)
6 months–6 years	10000 (6000–15000)	10 (6–15)
> 6 years	75000 (5000–10000)	7.5 (5–10)
Differential leukocyte count	*Percentage of total WBC count*	*Percentage of total WBC count*
Cord blood	N61 L31 E2 M6	N61 L31 E2 M6
0–12 weeks	N40 L48 E3 M9	N40 L48 E3 M9
3 months	N30 L63 E2 M5	N30 L63 E2 M5
6 months–6 years	N45 L48 E2 M5	N45 L48 E2 M5
7–12 years	N55 L38 E2 M7	N55 L38 E2 M7

Total neutrophil count	cells/mm³	X 10⁶ cells/L
Band cells	150–400	150–400
Segmented	3000–5800	3000–5800
Total lymphocyte count	cells/mm³	X 10⁶ cells/L
	1500–3000	1500–3000
Total monocyte count	cells/mm³	X 10⁶ cells/L
	285–500	285–500
Total eosinophil count	cells/mm³	X 10⁶ cells/L
	50–250	50–250
Total basophil count	cells/mm³	X 10⁶ cells/L
	15–50	15–50

MEASURES OF COAGULATION

Coagulation test	Value
Activated partial thromboplastin time (aPTT)	
Preterm neonate	35–100 s
Term neonate	35–70 s
1–5 years	24–36 s
6–10 years	26–36 s
11–16 years	26–37 s
Adult	27–40 s
Bleeding time (BT)	2–7 minutes
Clotting time (CT)	5–8 minutes
D-dimer	Positive titer = 1:8
Factor I/Fibrinogen	
Preterm neonate	1.2–3.8 g/L
Term neonate	1.5–3.5 g/L
Child	2.0–4.0 g/L
Adult	1.5–3.5 g/L
Fibrin degradation products (FDP)	207 (68–494) ng/L
Protein C (U/mL)	
Preterm neonate	0.28 (0.12–0.44)
Term neonate	0.35 (0.17–0.53)
1–5 years	0.66 (0.40–0.92)
6–10 years	0.69 (0.45–0.93)
11–16 years	0.83 (0.55–1.11)
Adult	0.96 (0.64–1.28)
Protein S Total (U/mL)	
Preterm neonate	0.26 (0.14–0.38)
Term neonate	0.36 (0.12–0.60)
1–5 years	0.86 (0.54–1.18)
6–10 years	0.78 (0.41–1.14)
11–16 years	0.72 (0.52–0.92)
Adult	0.81 (0.60–1.13)
Prothrombin time (PT)	
Preterm neonate	13–23 s
Term neonate	13–17 s
1–5 years	10.6–11.4 s
6–10 years	10.1–12.1 s
11–16 years	10.2–12.0 s
Adult	11.0–14.0 s
Reptilase time	
Preterm neonate	18–30 s
Term neonate	18–24 s
Adult	18–22 s
Thrombin time	
Preterm neonate	12–24 s
Term neonate	12–18 s
Adult	10–14 s

Coagulation Factors (% of Normal or Adult Value)

Coagulation factor	Preterm neonate	Term neonate	Children
Factor II	30–65	40–65	60–150
Factor V	50–100	50–100	60–150
Factor VII	20–150	40–70	65–135
Factor VIII	60–120	70–150	60–145
Factor IX	10–30	15–55	60–140
Factor X	10–45	20–55	60–130
Factor XI	10–50	15–70	65–135
Factor XII	20–50	25–70	65–150

SERUM BIOCHEMISTRY

Serum Proteins (g/dL)*

	Total proteins	Albumin	Globulins			
			α1	α2	B	γ
Preterm neonate	4.3–7.6	3.0–4.2	0.1–0.5	0.3–0.7	0.3–1.2	0.3–1.4
Term neonate	4.6–7.7	2.5–5.0	0.1–0.3	0.3–0.5	0.2–0.6	0.8–1.2
1–7 years	6.1–7.9	4.0–5.0	0.2–0.4	0.5–0.8	0.5–0.8	0.3–1.2
> 7 years	6.4–8.2	3.4–5.0	0.2–0.3	0.4–1.0	0.5–1.1	0.5–1.8

*SI units: g/L, multiplication factor 10.

		Conventional units	SI units, multiplication factor
Ammonia (Heparinized venous sample on ice analyzed within 30 min)		µg/dL	µmol/L, 0.7
Neonate		90–150	64–107
0–2 months		79–129	56–92
> 1 month		29–70	21–50
Adult		15–45	11–32
Bilirubin (serum), total		mg/dL	µmol/L, 17.1
Cord blood	Term	< 2	< 34
	Preterm	< 2	< 34
0–1 day	Term	< 8	< 137
	Preterm	< 6	< 103
1–2 days	Term	< 12	< 205
	Preterm	< 8	< 137
3–5 days	Term	< 16	< 274
	Preterm	< 12	< 205
Thereafter	Term	< 2	< 34
	Preterm	< 1	< 17
Adult		0.1–1.2	1.7–20.5
Bilirubin (serum), conjugated		0–0.4	0–8
Chloride (serum, heparinized plasma)		mEq/L	mmol/L, 1
Newborn		97–110	97–110
Thereafter		98–106	98–106

Contd...

Creatinine (serum)	mg/dL	µmol/L, 90
Neonate	0.3–1.0	27–88
Infant	0.2–0.4	18–35
Child	0.3–0.7	27–62
Adolescent	0.5–1.0	44–88

C-reactive protein	mg/dL	mg/dL, 1
0–90 days	0.08–1.58	0.08–1.58
90 days–3 years		
Male	0.08–1.12	0.08–1.12
Female	0.05–0.79	0.05–0.79
4–10 years		
Male	0.06–0.79	0.06–0.79
Female	0.5–1.0	0.5 –1.0
11–14 years		
Male	0.08–0.76	0.08–0.76
Female	0.06–0.71	0.06–0.71

Glucose (serum)	mg/dL	mmol/L, 0.0555
Preterm neonate	20–60	1.1–3.3
Term neonate	30–60	1.7–3.3
Newborn, day 1	40–60	2.2–3.3
Newborn > 1 day	50–90	2.8–5.0
Child	60–100	3.3–5.5
Adult	70–105	3.9–5.8
Glucose (whole blood, heparinized)		
Adult	65–95	3.6–5.3

Glucose tolerance test (Oral glucose: 1.75 g/kg, maximum 75 g)	mg/dL		mmol/L, 0.0555	
	Normal	Diabetic	Normal	Diabetic
Fasting	70–105	≥ 126	3.9–5.8	≥ 7.0
60 min	120–170	≥ 200	6.7–9.4	≥ 11
90 min	100–140	≥ 200	5.6–7.8	≥ 11
120 min	70–120	≥ 200	3.9–6.7	≥ 11

Lactate	mmol/L	mmol/L, 1
Whole blood lactate		
1–12 months	1.1–2.3	1.1–2.3
1 year	0.8–1.5	0.8–1.5
7–15 years	0.6–0.9	0.6–0.9
Plasma lactate		
6 months–3 years	0.0–0.3	0.0–0.3

Serum lipids		
Cholesterol	mg/dL	mmol/L, 0.0259
Cord blood	23–135	0.6–3.5
1–6 weeks	93–217	2.4–5.6
≥ 1 year	119–263	3.1–6.8
Phospholipids	mg/dL	g/L, 0.01
Cord blood	75–150	0.75–1.5
Neonate	170–250	1.7–2.5
> 1 month	150–300	1.5–3.0
Total lipids	mg/dL	g/L, 0.01
Newborn	150–400	1.5–4.0
> 1 month	400–1000	4.0–10.0
Free fatty acids	µEq/L	µmol/L
Newborn	250–1000	250–1000
> 1 month	300–1450	300–1450
Pyruvate (whole blood)	mmol/L	mmol/L, 1
7–17 years	0.076 (±0.026)	0.076 (±0.026)

Contd...

Urea (serum/plasma)	mg/dL	mmol/L, 0.357
Preterm neonate	3–25	1.1–9.0
Term neonate	3–12	1.1–4.3
Infant/child	5–18	1.8–6.4
Thereafter	7–18	2.5–6.4
Uric acid (serum)	mg/dL	mmol/L, 0.0595
	2–7	0.12–0.42

METALS AND BINDING PROTEINS

	Conventional units	SI units, multiplication factor
Serum ceruloplasmin	mg/dL	mg/L, 10
	21–53	210–530
Serum copper	µg/dL	µmol/L, 0.157
0–5 days	9–46	1.4–7.2
1–9 years	80–150	12.6–23.6
10–14 years	80–121	12.6–19
15–19 years	64–160	11.3–25.2
Serum folate	ng/mL	nmol/L, 2.265
	2.5–20	5.7–45.3
RBC folate	ng/mL RBCs	nmol/L cells
	150–450	340–1020
Serum iron	µg/dL	µmol/L, 0.179
Term neonate	100–250	18–45
Infant	40–100	7–18
Child	50–120	9–22
Adult, male	65–175	12–30
Adult, female	50–170	9–30
Total iron binding capacity (TIBC)	µg/dL	µmol/L, 0.179
Term neonate	150–200	26.8–35.8
Infant	200–400	35.8–71.6
Child	250–500	44.8–89.5
Adolescent	300–600	53.7–107.4
Adult	250–425	44.8–76.1
Serum transferrin	mg/dL	g/L, 0.01
Term neonate	130–275	1.3–2.75
Infant	200–360	2.0–3.6
Child	200–360	2.0–3.6
Adolescent	220–400	2.2–4.0
Adult	220–400	2.2–4.0
Serum ferritin	ng/mL	µg/L, 1
Term neonate	25–200	25–200
Infant	50–600	50–600
Child	7–140	7–140
Adolescent	7–140	7–140
Adult, male	20–250	20–250
Adult, female	10–120	10–120
Serum magnesium	mg/dL	mmol/L, 0.411
0–6 days	1.2–2.6	0.48–1.05
7 days–2 years	1.6–2.6	0.65–1.05
2–14 years	1.5–2.3	0.60–0.95
Blood lead	µg/dL	µmol/L, 4.8
Children	< 10	< 48
Adults	< 40	< 192
Toxic	≥ 70	≥ 336
Serum zinc	µg/dL	µmol/L, 0.153
	70–150	10.7–22.9

SERUM ENZYMES

Enzyme	Reference value
Amylase	U/L
1–19 years	30–100
Aldolase	U/L
10 months– 2 years	3.4–11.8
2 y–16 years	1.2–8.8
Alkaline phosphatase	U/L
Preterm neonate	Up to 1500
Term neonate	Up to 700
Infants	250–1000
2–5 years	250–850
6–7 years	250–1000
8–9 years	250–750
10–11 years, male	250–730
10–11 years, female	250–950
12–13 years, male	275–875
12–13 years, female	200–730
Acid phosphatase	0–0.8 U/L
Alanine aminotransferase (ALT,SGPT)	U/L
0–7 days	25–100
8–30 days	22–71
1–3 years	20–60
3–9 years	15–50
10–15 years	10–40
Aspartate aminotransferase (AST,SGOT)	U/L
0–7 days	25–100
8–30 days	22–71
1–3 years	20–60
3–9 years	15–50
10–15 years	10–40
Antistreptolysin O (ASO) titers*	Todd units
2–5 years	120–160
6–9 years	240
10–12 years	320
α1-Antitrypsin	0.93–2.24 g/L
Creatine kinase	U/L
Newborn	10–200
Adult	20–200

Creatine kinase isoenzymes	CKMB	CKBB
Cord blood	0.3–3.1%	0.3–10.5%
0–24 hours	1.7–7.9%	3.6–13.4%
72–100 hours	1.4–5.9%	5.1–13.3%
Older	0–2%	0

Gastrin	< 100 ng/L
Glucose 6 phosphate dehydrogenase (G6PD) Adult**	3.4–8.0 U/g hemoglobin or 1.16–2.72 U/mL RBC
γ-glutamyl transferase (GGT)	U/L
< 3 weeks	0–130
3 weeks–3 months	4–120
> 3 months, boy	5–65
> 3 months, girl	5–35
1–15 years	0–23
Adult, male	11–50
Adult, female	7–32
Lactate dehydrogenase (LDH)	U/L
< 1 years	170–580
1–9 years	150–500
10–19 years	120–330

Lactate Dehydrogenase, Isoenzymes (% total)	
LD1 heart	24–34%
LD2 heart, RBCs	35–45%
LD3 muscle	15–25%
LD4 liver, trace muscle	4–10%
LD5 liver, muscle	1–9%
Lipase	U/L
1–18 years	145–216

*4× rise in paired serial specimens is significant.
**Values are 50% higher in newborns.

NORMAL ACID BASE STATUS AND ELECTROLYTES

	Conventional units	SI units, multiplication factor
Anion gap	mEq/L	mmol/L, 1
[Sodium-(Chloride+Bicarbonate)]	7–16	7–16
Base excess	mmol/L	mmol/L
Newborn	–10 to –2	–10 to –2
Infant	–7 to –1	–7 to –1
Child	–4 to +2	–4 to +2
Older	–3 to +3	–3 to +3
Bicarbonate, serum	mEq/L	mmol/L, 1
Arterial	21–28	21–28
Venous	22–29	22–29
Calcium, total, serum	mg/dL	mmol/L, 0.25
< 24 hours	9.0–10.6	2.3–2.65
24–48 hours	7.0–12.0	1.75–3.0
4–7 days	9.0–10.9	2.25–2.73
Child	8.8–10.8	2.2–2.7
Calcium, ionized, serum	mg/dL	mmol/L, 0.25
< 24 hours	4.3–5.1	1.07–1.27
24–48 hours	4.0–4.7	1.0–1.17
Child	4.8–4.92	1.12–1.23
Carbon dioxide, total (tCO$_2$)	mmol/L	mmol/L, 1
Cord	14–22	14–22
Newborn	13–22	13–22
Infant	20–28	20–28
Child	20–28	20–28
Carbon dioxide partial pressure, arterial (PaCO$_2$)	mm Hg	kPa, 0.1333
Newborn	27–40	3.6–5.3
Infant	27–41	3.6–5.5
Thereafter, males	35–48	4.7–6.4
Thereafter, females	32–45	4.3–6.0
Chloride, serum	mEq/L	mmol/L
	95–106	95–106
Osmolarity, serum	mosm/L	mosm/L
	275–290	275–290
Oxygen partial pressure (PaO$_2$), arterial	mm Hg	kPa, 0.1333
Birth	8–24	1.1–3.2
5–10 min	33–75	4.4–10
30 min	31–85	4.1–11.3
> 1 hour	55–80	7.3–10.6
1 day	54–95	7.2–12.6
Thereafter	83–108	11–14.4

Oxygen saturation (SaO₂), arterial	%	Fraction saturation, 0.01
Newborn	85–90	0.85–0.90
Thereafter	95–99	0.95–0.99
pH, arterial		
Birth	7.11–7.36	7.11–7.36
24 hours	7.3–7.45	7.3–7.45
Older	7.35–7.45	7.35–7.45
Potassium, serum	mEq/L	mmol/L, 1
< 2 months	3–7	3–7
2–12 months	3.5–6	3.5–6
> 12 months	3.5–5	3.5–5
Sodium, serum	mEq/L	mmol/L
Newborn	134–146	134–146
< 1 year	139–144	139–144
Child	138–145	138–145

HORMONES IN SERUM AND URINE

	Conventional units	SI units, multiplication factor
Adrenocorticotrophic hormone (ACTH), plasma	pg/mL	ng/L, 1
Cord blood	130–160	130–160
1–7 days postnatal	100–140	100–140
Adult		
morning	25–100	25–100
evening	< 50	< 50
Aldosterone, plasma/serum	ng/dL	nmol/L, 1
1–12 months	5–90	1.4–2.5
1–2 years	7–54	0.19–1.5
2–10 years	3–35	0.1–0.97
10–15 years	2–22	0.1–0.6
Aldosterone, urine	µg/24 hours	nmol/24 hours, 2.78
Newborn	0.5–5	1.39–13.9
4–10 years	1–8	2.78–22.2
Older	3–19	8.3–52.8
Antidiuretic hormone (ADH), plasma varies with plasma osmolarity (mosm/kg)	pg/mL	pg/mL, 1
270–280	< 1.5	< 1.5
280–285	< 2.5	< 2.5
285–290	1–5	1–5
290–295	2–7	2–7
295–300	4–12	4–12
Calcitonin, plasma	pg/mL	pmol/L, 0.28
Newborn	70–348	19.6–97.4
Males	3–26	0.8–7.2
Females	2–17	0.6–4.7
Catecholamines, serum	µg/24 hours	µg/24 hours, 1
Dopamine	100–440	100–440
Epinephrine	< 15	< 15
Norepinephrine	15–86	15–86
Metanephrines	< 0.4	< 0.4
Normetanephrines	< 0.9	< 0.9
Homovanillic acid (HVA)	0–10	0–10
Vanillyl mandelic acid (VMA)	2–10	2–10

Cortisol, plasma	µg/dL	nmol/L, 27.59
Newborn	1–24	28–662
Adults		
Morning 8 a.m.	5–23	138–635
Evening 4 p.m.	3–15	82–413
Night 8 p.m.	Less than 50% of morning level	Less than 50% of morning level
Cortisol, free, urine	µg/24 hours	nmol/24 hours, 2.75
Child	2–27	5.5–74.2
Adolescent	5–55	13.7–151.25
Dehydroepiandrosterone (DHEA) sulfate, serum	µg/dL	nmol/L, 2.714
Newborn	1.7–3.6	4.6–9.7
Prepubertal	0.1–0.6	0.27–1.6
Men	1.4–7.9	3.7–21.4
Women	0.7–4.5	1.9–12.2
Dihydrotestosterone (DHT), serum	ng/dL	–
Prepubertal, males	< 3–13	
Prepubertal, females	< 3–10	
Tanner 2, males	5–17	
Tanner 2, females	4–12	
Tanner 3, males	7–35	
Tanner 3, females	9–21	
Tanner 4, males	12–52	
Tanner 4, females	9–23	
Tanner 5, males	13–17	
Tanner 5, females	< 3–36	
Adults, males	30–100	
Adults, females	6–33	
Estradiol, serum	pg/mL	pmol/L, 3.571
Prepubertal	< 25	< 89.2
Men	6–44	21.4–157.1
Women	15–260 (Luteal)	53.6–928.5
	10–200 (Follicular)	35.7–714.2
	120–375 (Midcycle)	
		428.5–1339.1
Gonadotropins, serum	mIU/mL	–
FSH		
Prepubertal	0–2.8	
Men	1.4–14.4	
Women, follicular	3.7–12.9	
LH		
Prepubertal	0–1.6	
Men	1–10.2	
Women, follicular	0.9–14	
Growth hormone, plasma	ng/mL	µg/L, 1
1 day	5–53	5–53
1 week	5–27	5–27
1–12 months	2–10	2–10
Child	0.7–6	0.7–6
Adult	0.7–6	0.7–6
5–Hydroxyindoleacetic acid (HIAA), urine	mg/24 hours	–
	2–8	
17-Hydroxycorticosteroid, urine	mg/24 hours	
Infant	0–1.0	
Child	1.0–5.6	
Adult, male	3–10	
Adult, female	2–8	

17-Hydroxyprogesterone, serum	ng/L	ng/L, 1
Prepubertal		
Males	0–81	0–81
Females	0–92	0–92
Adult		
Males	36–154	36–154
Females	15–102 (follicular)	15–102 (follicular)
	150–386 (luteal)	150–386 (luteal)

17-Ketosteroids, urine	mg/24 hours	–
< 1 month	< 2.0	
1 month–5 years	< 0.5	
6–8 years	1.0–2.0	
Men	9–22	
Women	5–15	

Insulin, plasma (12 hours fasting)	µU/mL	pmol/L, 7.14
Newborn	3–20	21–143
Thereafter	7–24	50–171

Prolactin, serum	µg/L	pmol/L, 42.5
Male	< 15	< 652
Female	< 20	< 850

Parathormone, serum	pg/mL	pg/mL, 1
Intact	< 10–65	< 10–65
C-terminal	50–340	50–340
N-terminal	4–19	4–19

Renin activity, plasma	nmol/L/hour	nmol/L/hour, 1
0–6 days	2.8–79	2.8–79
6 days–1 years	6.4–27.2	6.4–27.2
2–4 years	1.5–22.6	1.5–22.6
5–9 years	1.8–7.2	1.8–7.2
10–15 years	0.7–7.8	0.7–7.8

Testosterone, total, serum	ng/dL	nmol/L, 0.0347
Prepubertal	10–20	0.3–0.6
Men	275–875	9.5–30.4
Women	23–75	7.9–2.6
Pregnant females	35–195	1.2–6.7

Thyroxine (T₄), serum	ng/dL	pmol/L, 13
Free T₄		
1–10 days	0.6–2.0	7.8–26
> 10 days	0.7–1.7	9.1–22.1
Total T₄, by RIA	µg/dL	pmol/L, 13
Cord	6.6–17.5	85.8–227.5
1–3 days	11.0–21.5	143–279.5
1–4 weeks	8.2–16.6	106.6–215.8
1–12 months	7.2–15.6	93.6–202.8
1–5 years	7.3–15.0	94.9–195
6–10 years	6.4–13.3	83.2–172.9
11–15 years	5.6–11.7	72.8–152.1
16–20 years	4.2–11.8	54.6–153.4
21–50 years	4.3–12.5	56–162.5

Triiodothyronine (T₃), serum, by RIA	ng/dL	nmol/L, 0.015
Cord	14–86	0.2–1.3
1–3 days	100–380	1.5–5.7
1–4 weeks	99–310	1.5–4.6
1–12 months	102–264	1.5–3.9
1–5 years	105–269	1.6–4.1
6–10 years	94–241	1.4–3.6
11–15 years	83–213	1.2–3.2
16–20 years	80–210	1.2–3.1
21–50 years	70–204	1.0–3.1

Thyroid stimulating hormone (TSH), serum	µIU/mL	–
Cord	< 2.5–17.4	
1–3 days	< 2.5–13.3	
1–4 weeks	0.6–10.0	
1–15 years	0.6–6.3	
16–50 years	0.2–7.6	

Thyoxine-binding globulin (TBG), serum	mg/dL	mg/L, 10
Cord	0.7–4.7	7–47
1–3 days	–	–
1–4 weeks	0.5–4.5	5–45
1–12 months	1.6–3.6	16–36
1–15 years	1.3–2.8	13–28
16–20 years	1.4–2.6	14–26
21–50 years	1.2–2.4	12–24

T3, reverse, serum	ng/dL	–
Newborn	90–250	
Children	10–50	
Adult	10–50	

NORMAL URINARY VALUES

Volume	mL
Neonate	50–300
Infant	350–550
Child	500–1000
Adolescent	700–1400

Specific gravity	
24 hours	1.015–1.025
After fluid restriction for 12 hours	> 1.025

Osmolality	mosm/kg
24 hours	50–1400
After fluid restriction for 12 horus	>850

pH	
Neonate	5–7
Child	4.5–8

Cell count	Cells/hpf
Red blood cells	0–2
White blood cells	0–5
Epithelial cells	A few
Bacteria	0–20 in centrifuged specimen

Casts	Per hpf
Hyaline casts	0–1
RBC, WBC, epithelial casts	Absent

Ammonia	mEq/min/m²
2–12 months	4–20
1–16 years	6–16

Creatinine	mg/kg/24 hours
Newborns	7–10
Children	20–30
Adult males	21–26
Adult females	16–22

Contd...

Glomerular filtration rate	mL/min/1.73 m²
Neonate < 34 weeks' gestation	
2–8 days	11 (11–15)
4–28 days	20 (15–28)
30–90 days	50 (40–65)
Neonate >34 weeks' gestation	
2–8 days	39 (17–60)
4–28 days	47 (26–68)
30–90 days	58 (30–86)
1–6 months	7 (39–114)
6–12 months	103 (49–157)
12–19 months	127 (62–1910)
2 years–Adult	127 (89–165)
Growth hormone	
2.2–13.3 years (Tanner 1)	0.4–6.3 ng/24 hours (0.9–12.3 ng/g creatinine)
10.3–14.6 years (Tanner 2)	0.8–12.0 ng/24 hours (1.0–14.1 ng/g creatinine)
11.5–15.3 years (Tanner 3)	1.7–20.4 ng/24 hours (1.9–17.0 ng/g creatinine)
12.7–17.1 years (Tanner 4)	1.5–18.2 ng/24 hours (1.3–14.4 ng/g creatinine)
13.5–19.9 years (Tanner 5)	1.2–14.5 ng/24 hours (0.8–11.0 ng/g creatinine)
Porphyrins	
α-Aminolevulinic acid	0–7 mg/24 hours (0–53.4 mol/24 hours)
Porphobilinogen	0–2 mg/24 hours (0–8.8 mol/24 hours)
Coproporphyrin	0–160 mg/24 hours (0–244 mol/24 hours)
Uroporphyrin	0–26 mg/24 hours (0–31 mol/24 hours)
Sodium	
24 hours sample	41—115 mmol/24 hours
Spot sample	>20 mmol/L
Potassium	mmol/L
24 hours sample	10–60
Chloride	mmol/24 hours
Infant	2–10
Child	15–40
Calcium	
24 hours sample	100–250 mg (2.5–6.2 mmol)
Calcium: creatinine	(mg/mg ratio)
< 7 months	0.86
7–18 months	0.6
19 months–6 years	0.42
Adults	0.22
Protein	mg/24 hours
Total (24 hours)	
At rest	50–80
Following exercise	Up to 250
Glucose	
Qualitative estimation	Nil
Quantitative estimation	0.5 g/24 hours
Galactose	mg/dL
Neonate	< 60
Child	14
Copper	mg/mol creatinine
	0.36–7.56
Coproporphyrin	µg/24 hours
	34–234

Contd...

Total free catecholamines	µg/24 hours
0–1 year	10–15
1–5 years	15–40
6–15 years	20–80
Homovanillic acid (HVA)	mg/g creatinine
0–1 year	< 32.2
2–4 years	< 22
5–19 years	< 14
Vanillyl mandelic acid (VMA)	mg/g creatinine
0–1 year	< 18.8
2–4 years	< 11.0
5–19 years	< 8.0
Mucopolysaccharides	µg/g creatinine
0–2 years	< 50
2–4 years	< 25
4–15 years	< 20

Hemoglobin, bilirubin, ketones, myoglobin, porphobilinogen and glucose are undetectable in normal urine by qualitative tests.

CEREBROSPINAL FLUID

Opening pressure	mm Hg
Newborn	80–110
Infant/child	< 200
Respiratory variation	5–10
WBC count	Cells/mm³
Preterm mean (range)	9 (0–25), 57% polymorphs
Term mean (range)	8 (0–22), 61% polymorphs
Child	0–7, 0% polymorphs
Glucose*	mg/dL
Preterm mean (range)	50 (24–63)
Term mean (range)	52 (34–119)
Child	40–80
Protein	mg/dL
Preterm mean (range)	115 (65–150)
Term mean (range)	90 (20–170)
Child	5-40
Lactic acid dehydrogenase	U/L
	20 (5–30), or about 10% of serum value
Myelin basic protein	ng/mL
	< 4
Chloride	mmol/L
	118–132
Lactate	mmol/L
	0.8–2.4

*CSF glucose is at least 50–70% of corresponding blood sugar.

STOOL SPECIMEN

pH	7.0–7.5
Fecal fats (Measured over 72 hours)	g/24 hours
Breastfed infant	< 1
0-6 years	< 2
Fecal bile acids	mg/24 hours
	120–225
Fecal a1 antitrypsin	mg/g of stool
Breastfed infant	< 4.4
Top fed infant	< 2.9
6 months–4 years	< 1.7
Occult blood	Negative (< 2 mL/24 hours in 100–200 g of stool)
Ova and cysts	Nil

AMNIOTIC FLUID

αFetoprotein	µg/mL
15 weeks' gestation	13.5 ± 3.42
16 weeks' gestation	11.7 ± 3.38
17 weeks' gestation	10.3 ± 3.03
18 weeks' gestation	9.5 ± 3.22
19 weeks' gestation	7.1 ± 2.85
20 weeks' gestation	5.0 ± 2.45
Creatinine	mg/dL
	> 2 (After term gestation)
Lecithin	mg/dL
	> 0.1 indicates fetal lung maturity
Lecithin/sphinogomyelin (LS ratio)	> 2:1 indicates fetal lung maturity
Total bilirubin	mg/dL
28 weeks' gestation	< 0.075
40 weeks' gestation	< 0.025

SWEAT

Sweat Chloride Test

Value	Interpretation
< 40 mmol/L	Normal
40–60 mmol/L	Borderline
≥ 60 mmol/L	Cystic fibrosis

SERUM VITAMIN LEVELS

Vitamin	Conventional units	SI units
Vitamin A/Retinol	µg/dL	µmol/L
Newborn	35–75	1.22–2.62
Child	30–80	1.05–2.79
Adult	30–65	1.05–2.27
Vitamin B$_1$/Thiamine	µg/dL	µmol/L
	5.3–7.9	0.16–0.23
Vitamin B$_2$/Riboflavin	µg/dL	µmol/L
	3.7–13.7	98–363
Vitamin B$_6$/Pyridoxine	ng/mL	nmol/L
	5–24	30–144
Vitamin B$_{12}$/Cobalamin	pg/mL	pmol/L
	130–785	96–579
Vitamin C/Ascorbic acid	mg/dL	µmol/L
	0.2–2	11.4–113.6

Contd...

Vitamin D2	pg/mL	pmol/L
	24–65	58–156
Vitamin D3/Calcitriol	pg/mL	pmol/L
	25–45	60–108
Vitamin E	mg/dL	µmol/L
	5–20	10.7–22.9
Folate, serum	ng/mL	nmol/L
	> 1.9	> 4.3

SERUM IMMUNOGLOBULIN LEVELS

Age	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgE (IU/mL)
Cord blood (term)	1121 (636–1606)	1.3 (6.3–25)	2.3 (1.4–3.6)	-
1 month	503 (251–906)	45 (20–87)	13 (1.3–53)	-
6 month	407 (215–704)	62 (35–102)	25 (8.1–68)	2.68 (0.44–16.3)
1 year	679 (345–1213)	93 (43–173)	44 (14–123)	3.49 (0.80–15.2)
2 years	685 (424–1051)	95 (48–168)	47 (14–123)	3.03 (0.31–29.5)
3 years	728 (441–1135)	104 (47–200)	66 (22–159)	1.80 (0.19–16.9)
4–5 years	780 (463–1236)	99 (43–196)	68 (25–154)	8.58 (1.07–68.9)
6–8 years	915 (633–1280)	107 (48–207)	90 (33–202)	12.89 (1.03–161.3)
9–10 years	1007 (608–1572)	121 (52–242)	113 (45–236)	23.66 (0.98–570.6)
Adult	994 (639–1349)	156 (56–352)	171 (70–312)	13.2 (1.53–114.0)

Values expressed in mean (95% CI).
Immunoglobulin D: Newborn: 0 mg/dL; Thereafter: 0-8 mg/dL.

MORE ON THIS TOPIC

Arcara K, Tschudy M. The Harriet Lane handbook: a manual for pediatric house officers. Philadelphia: Mosby Elsevier.19th ed;2012.

Jolliff CR, Cost KM, Stivrins PC, et al. Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. Clin Chem.1982;28:126-8.

Kjellman NM, Johansson SG, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). Clin Allergy.1976;6:51-9.

Kliegman RM, Stanton BF, St. Gemell JW. Nelson Textbook of Pediatrics. Philadelphia: Saunders Elsevier; 19th ed; 2011.

Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. J Pediatr.1993;123:393-7.

Annexure B
Drug Doses
Pooja Dewan, Nidhi Bedi

ANTIARRHYTHMICS

Adenosine
Intravenous; ampoule (3 mg/mL).

Supraventricular tachycardia 0.1–0.2 mg/kg rapid intravenous push over 1–2 seconds, may increase bolus dose by 0.05 mg/kg every 2 min till clinical response or maximum of 12 mg (0.25 mg/kg). Follow each dose with a normal saline flush.

Adverse effects Bronchoconstriction, facial flushing, headache, chest pain, dyspnea.

Contraindications 2nd and 3rd degree heart block or sick sinus syndrome unless pacemaker placed.

Atropine Sulfate
Oral, intravenous; Tablets (0.4 mg, 0.6 mg), ampoule (0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1 mg/mL).

Cardiac resuscitation 0.02 mg/kg/dose IV every 5 min × 2-3 doses, maximum dose in children: 1 mg, in adolescents: 2 mg.

Preanesthesia dose Child: 0.01 mg/kg/dose SC/IV/IM, maximum: 0.4 mg/dose; minimum: 0.1 mg/dose, may repeat q 4–6 h.

Contraindications Glaucoma, tachyarrhythmias, thyrotoxicosis.

Lignocaine Hydrochloride
Intravenous; 2% solution (20 mg/mL) 1 mg/kg/dose IV slowly (can repeat in 5–10 min X 2; maximum 3 mg/kg) loading followed by 20–50 μg/kg/min as maintenance.

Contraindication Stokes–Adams attacks, SA, AV, or intraventricular heart block without pacemaker.

Adverse effects Hypotension, asystole, seizures and respiratory arrest.

Phenytoin Sodium
Antiarrhythmic (secondary to digitalis intoxication)
Intravenous, oral; Ampoule (50 mg/mL), syrup or suspension (125 mg/5 mL, 30 mg/5 mL), Tablet (100 mg).

Loading dose 1.25 mg/kg IV q 5 min (maximum 15 mg/kg); Maintenance dose: 5–10 mg/kg/day q 12 h IV/PO.

Contraindication Heart block or sinus bradycardia.

Adverse effects Nystagmus, hypotension, Steven-Johnson syndrome, rash, hepatitis, gingival hyperplasia, blood dyscrasia.

Procainamide Hydrochloride
Intramuscular, intravenous, oral; Tablet (250 mg, 375 mg, 500 mg), injection (100 mg/mL, 500 mg/mL).

IM 20–30 mg/kg/day q 4–6 h, maximum dose 4 g/day
IV: Load: 2–6 mg/kg/dose over 5 min (maximum 100 mg); Maintenance dose: 20–80 μg/kg/min by continuous infusion, maximum dose 2 g/day.
Oral: 20–30 mg/kg/day q 3–6 h (maximum 4 g/day).
Contraindication Complete heart block, SLE, myasthenia gravis, torsades de pointes.

Adverse effects Hypotension, atrioventricular block, arrhythmias, SLE like syndrome, agranulocytosis.

Propranolol
Oral, intravenous; Tablet (10 mg), ampoule (1 mg/mL)
Supraventricular tachycardia: Oral: 0.25 mg/kg/dose q 6–8 h.
Intravenous: 0.01–0.1 mg/kg/dose over 10–15 min, repeat q 6–8 h.

Thyrotoxicosis Neonates: 0.5 mg/kg/dose orally q 6 h; children: 0.5–1 mg/kg/dose orally q 6 h.

Migraine prophylaxis 0.5–2 mg/kg/day orally q 6–8 h.

Contraindication Heart block, heart failure and Raynaud's syndrome, asthma.

Verapamil
Oral, intravenous; Tablet (40, 80 mg), ampoule (2.5 mg/mL).

IV Infants: 0.1–0.2 mg/kg IV over 2–3 min using continuous ECG monitoring. May repeat after 30 min; children: 0.1–0.3 mg/kg maximum dose: 5 mg.

PO 1–2 mg/kg/dose q 6–8 h.

Contraindication Hypersensitivity, cardiogenic shock, severe CHF, sick–sinus syndrome or AV block. Avois IV use in neonates and young infants due to apnea, bradycardia, and hypotension.

Antidote Calcium gluconate.

ANTIASTHMATICS AND BRONCHODILATORS

Adrenaline
Intravenous, subcutaneous, intramuscular, intratracheal; Ampoule (1:1000 solution, 1 mL = 1 mg).

Subcutaneous/intramuscular 0.01 mL/kg 1:1000 solution, max 0.5 mL per dose.
Intravenous/endotracheal: 0.1 mL/kg of 1:10,000 solution
Dilute in normal saline.

Adverse effects Tachycardia, restlessness, hypertension, tremors.

Aminophylline
Oral, intravenous; Syrup (20 mg/5 mL), ampoule (250 mg/10 mL)

Bronchospasm Loading 5 mg/kg IV over 30 min followed by
0.5 mg/kg/h: 6 weeks–6 months; 0.7 mg/kg/h: 6 months–1 year; 1 mg/kg/h: 1–9 years; 0.9 mg/kg/h: 9–12 years

Apnea of prematurity 6 mg/kg IV/PO loading followed by 2 mg/kg/dose q 8–12 h

Adverse effects Arrhythmia, seizure, GERD.

Caution Narrow therapeutic range. Therapeutic range: 5–15 μg/mL.

Bambuterol
Oral; Syrup (5 mg/5 mL), tablets (10, 20 mg)
2–5 years: 5 mg OD; 6–12 years: 10 mg OD.

Beclomethasone Dipropionate
Inhalational; MDI (50, 100, 200 μg/puff), rotacaps (100, 2000, 400 μg)
200–1000 μg/day in 2–4 divided doses
Adverse effects Hoarsness, oral candidiasis.

Budesonide
Inhalational; MDI (100, 200 μg/puff), rotacaps (100, 2000, 400 μg, nebulizing solution (250 μg/mL)

BPD 400 µg/kg inhaled twice daily. Asthma: Aerosol 1–12 years: 50–400 µg; 12–18 years: 200–400 µg. Start at 100 µg twice a day; up to maximum of 800 µg/day. Nebulization: 3 months–12 years: 250–500 µg twice daily; 12–18 years: 500 µg–1000 µg twice daily

Adverse effects Pharyngitis, cough, epistaxis, nasal irritation, rinse mouth after each use of MDI.

Formoterol Fumarate
Inhalational; MDI (12 µg/puff), rotacaps (6 µg)
MDI 12 µg BD.

Fluticasone Propionate
Inhalational; MDI (25, 50, 125 µg/puff)
MDI 50–500 µg/day in two divided doses.

Ipratropium Bromide
Inhalational; nebulizing solution (250 µg/mL), MDI (20 µg/puff)

Nebulized dose < 1 year: 125 µg/dose; > 1 year: 250 µg/dose. Nebulized after dilution in 2–4 mL of saline and given over 10 min every 20 min for 3 doses followed by nebulization every 2–4 hours.

Inhaler dose < 12 y: 1–2 puffs 3–4 times a day;
              ≥ 12 y: 2–3 puffs 4 times a day

Levosalbutamol
Oral, inhalational; Syrup (1 mg/5 mL); nebulizing respules (0.31, 0.63, 1.2 mg/2.5 mL)
Oral: 0.05–0.1 mg/kg/dose 2–3 times/day; nebulization: 0.075 mg/kg/dose.

Magnesium Sulfate
Intravenous ampoule (50% sol; 1 mL = 500 mg)
25–50 mg/kg/dose IV infusion over 20 minutes (max–2 g)
Respiratory depression if given in overdose.

Montelukast Sodium
Oral; Tablet (4 mg, 5 mg, 10 mg)
2–5 years: 4 mg once in the evening; 6–14 years: 5 mg once in the evening; > 15 years: 10 mg once in the evening

Adverse effects Headache, dizziness, fatigue, elevated liver enzymes.

Salbutamol
Oral, inhalational; Syrup (2 mg/5 mL), nebulizing solution (5 mg/mL), MDI (100 µg/puff).

Oral 0.1–0.2 mg/kg/dose 2–3 times/day; nebulization: 0.15 mg/kg/dose; min–1.25 mg; max– 3 mg.

Acute exacerbation 2–4 puffs by MDI every 20 min followed by 2 puffs every 4–6 h.

Adverse effects Tachycardia, tremors, hypokalemia.

Salmeterol
Inhalational; MDI (25 µg/puff, 50–100 µg/day)

Caution Not to be used in treatment of acute asthma. Not to be used as monotherapy. Not to be used in children < 4 years.

Terbutaline
Oral, intravenous, subcutaneous; Syrup (1.5 mg/mL); ampoule (0.5 mg/mL), tablets (2.5, 5 mg), MDI (250 µg/puff), nebulizing solution (10 mg/mL).

Oral 0.05 mg/kg/dose (max 5 mg) 3 times/day; SC: 0.005–0.01 mg/kg/dose, (0.01–0.02 mL/kg/dose) up to 4 times/day. Inhale 1–2 puffs of 250 µg q 6–8 h. Nebulization: 2.5 mg in children below 20 kg and 5 mg in children >20 kg.

Adverse effects Tachycardia, arrhythmias, flushing, headache, tremors, hypokalemia.

Theophylline
Oral; Tablets (100, 150, 200, 250, 400, 600 mg), syrup (80 mg/15 mL, 50 mg/5 mL)
15–25 mg/kg/day q 8 h PO.

ANTIFUNGALS

Amphotericin B
Oral, intravenous; Suspension (100 mg/mL), tablet (100 mg), Vial (50 mg/vial, liposomal: 10, 25, 50 mg)
Start at 0.25 mg/kg and increase till 1 mg/kg/day OD as infusion in 5% dextrose.

Liposomal 3–5 mg/kg/day OD

Caution Protect from light, nephrotoxic. Monitor serum potassium levels. IV administration may cause chills, fever, vomiting and headache, may premedicate with pethidine.

Clotrimazole
Topical application; available as lotion, gel, mouth paint, powder, vaginal pessaries

Apply locally 3–4 times per day.

Caspofungin
Intravenous; Vial (50 mg, 70 mg)
Loading dose 70 mg/m^2 on day 1, followed by 50 mg/m^2/day OD.

Fluconazole
Intravenous, Oral; Injection (200 mg/100 mL), tablet (50, 150 mg)
3–6 mg/kg/day OD

In neonates, loading dose 12 mg/kg followed by 3–5 mg/kg/day OD.

Griseofulvin
Oral; Tablet (125, 250, 500 mg)
10 mg/kg/day q 6–12 hours PO.

Itraconazole
Oral, injection; Capsule (100 mg), oral solution (10 mg/mL), injection (10 mg/mL)
200–400 mg/day q 12–24 h

Oral solution is used for treating oral candidiasis.

Ketoconazole
Topical, oral; Available as cream, shampoo, tablet (200 mg), syrup (100 mg/5 mL)
3.5–6.5 mg/kg/day OD.

Voriconazole
Intravenous, oral; Tablet (50, 200 mg), vial (200 mg/vial)

Load 6 mg/kg IV q 12 h on day 1 followed by 4 mg/kg/day q 12 h. Consume 1 h before or 2 h after meals.
For aspergillosis, invasive candidemia

2–11y: 9 mg/kg IV/PO every 12 h
≥12 y: 6 mg/kg every 12 h IV/PO for 2 doses, followed by 4 mg/kg IV/PO every 12 h

ANTI-INFLAMMATORY, ANTIPYRETICS, AND ANALGESICS

Acetaminophen (Paracetamol)

Oral, intravenous; Drops (150 mg/mL) syrup (125 mg/5 mL, 250 mg/5 mL), Tablet (500 mg, 650 mg), ampoule (150 mg/mL)

Dose 10–15 mg/kg/dose q 4–6 h PO, injection 5 mg/kg IM single dose

Excessive intake causes hepatic necrosis. In acute overdose N–acetylcysteine is the antidote.

Acetyl Salicylic Acid (Aspirin)

Oral; Tablet (75 mg, 100 mg, 325 mg, 650 mg)

Fever 10–15 mg/kg/dose 4–6 times/day; anti-inflammatory dose: 80–100 mg/kg/day in 3–4 divided doses. Kawasaki: 25 mg/kg/dose QID, Antiplatelet dose: 3–5 mg/kg/day OD, rheumatic fever: 100 mg/kg/day for 2–3 weeks followed by 60 mg/kg/day for the next 9–12 weeks.

Codeine Phosphate

Oral, tablet (15 mg, 30 mg, 60 mg), syrup

Pain 0.5–1 mg/kg/dose q 4–6 h, maximum 60 mg/dose

Cough 1–1.5 mg/kg/24 h q 4–6 h

Adverse effects Constipation, drowsiness.

Diclofenac Sodium

Oral, intramuscular; Tablet (50 mg, 75 mg, 100 mg), injection (75 mg per 3 mL ampoule)

Dose 1–3 mg/kg/day in 2–4 divided doses

Adverse effects Dizziness, headache, fluid retention, gastric bleeding or ulcer.

Fentanyl

Intravenous, oral; Ampoule (50 µg/mL), oral lozenges (200, 300, 400 µg)

Infants 1–4 µg/kg/dose q 1–4 h IV; Continuous infusion 0.5–5 µg/kg/h

Children 1–3 µg/kg/dose q 1–4 h IV; Continuous infusion 1–5 µg/kg/h

PO 10–15 µg/kg/dose, max 400 µg/dose

Adverse effects Hypotension, bradycardia, GI upset, respiratory depression, biliary tract spasm.

Ibuprofen

Oral, intravenous; Syrup (100 mg/5 mL); Tablet (200 mg), injection (10 mg/mL in 2 mL vials)

For fever/analgesia 10–15 mg/kg/dose q 4–6 h, maximum 60 mg/kg/day. For JRA: 30–70 mg/kg/d q 4–6 h, oral. For ductus closure: 10 mg/kg IV followed by 5 mg/kg IV every 24 h for 2 doses.

Adverse effects Abdominal cramps, nausea, heartburn, fluid retention.

Indomethacin

Oral, intravenous; Capsule (25 mg, 50 mg), Injection (1 mg vial)

3 mg/kg/d q 8 h, oral. For duct closure in preterm neonate: 0.2 mg/kg/dose IV 8 h for 3 doses.

Avoid in neonates with NEC, poor renal function, or active bleeding.

Mefenamic Acid

Oral; Tablet (100 mg), capsule (250 mg, 500 mg), suspension (100 mg/5 mL, 50 mg/5 mL)

For arthritis 25 mg/kg/d q 6 h, for fever: 3 mg/kg/dose

Side effects include diarrhea, skin rash and gastritis. Administer with food. Avoid in patients having seizures.

Morphine Sulfate

Subcutaneous injection, occasionally intravenously
Ampoule (10 mg, 15 mg, 25 mg per mL)

0.1–0.2 mg/kg/dose SC, maximum 15 mg. Occasionally used IV 2–5 mg/dose for preoperative medication, postoperative pain, restlessness, pulmonary edema. For continuous infusion in neonates 0.01–0.02 mg/kg/h, infants and children 0.025–0.2 mg/kg/h.

Antidote Naloxone.

Naproxen

Oral, tablet (250 mg) for analgesia 5–7 mg/kg/dose q 8–12 h, for JRA: 10–20 mg/kg/d q 12 h

Adverse effects Dizziness, rash, gastric irritation.

Pentazocine Hydrochloride

Oral, intravenous, intramuscular; Tablet (25 mg; 15 mg pentazocin with 500 mg paracetamol), ampoule (30 mg/mL)

0.5–1.0 mg/kg/d q 4 h oral, IM or IV (Maximum dose 30 mg IV)
Contraindications Raised intracranial tension, head injury.

Piroxicam

Oral; Capsule (20 mg)

0.2–0.3 mg/kg/24 h (max 15 mg/kg/24 h).

Prednisolone

Oral, tablets (5 mg, 10 mg, 20 mg), syrup (5 mg/5 mL)

1–2 mg/kg/day q 6–12 h

Adverse effects Edema, hypertension, cushing syndrome, peptic ulcer, hypothalamic pituitary–adrenal axis suppression.

ANTIBIOTICS: AMINOGLYCOSIDES

Amikacin Sulfate

Intravenous, intramuscular; Vial (100, 250, 500 mg)
15–20 mg/kg/day q 8–12 h.

Gentamicin Sulfate

Intravenous; intramuscular; Ampoule (10, 40 mg/mL)
5.0–7.5 mg/kg/day q 8–12 h

Kanamycin Sulfate

Intravenous, intramuscular; Vial (500 mg, 1 g)
15 mg/kg/day q 8–12 h IM, IV given over 30–60 min; Used for MDR TB

Netilmicin Sulfate

Intravenous, intramuscular; ampoule (10, 25, 50, 100 mg/mL)
5–7.5 mg/kg/day q 8–12 h (infants 7.5–10 mg/kg/day)

Streptomycin Sulfate

Intravenous, Intramuscular; Vial (750 mg, 1 g)
20–40 mg/kg/day q 12 h IV or single dose IM

Tobramycin

Intravenous, intramuscular; vials (20 mg, 40 mg, 80 mg in 2 mL vial)
6–7.5 mg/kg/day q 8–12 h IV, IM

Adverse effects Nephrotoxicity, hearing loss

CEPHALOSPORINS

Cefazolin Sodium
Intravenous; Intramuscular; Vial (250, 500 mg, 1g)
50–100 mg/kg/day q 6 h IV/IM

Cefepime
Intravenous; Vial (250, 500 mg, 1g)
100 mg/kg/day q 8–12 h IV/IM
For meningitis/serious infections 150 mg/kg/d q 8 h

Cefixime
Oral; Syrup (50 mg/5 mL), tablet (100, 200,400 mg)
8–10 mg/kg/day q 12 h; enteric fever: 15–20 mg/kg/day q 12 h

Cefoperazone Sulbactam
Intravenous; vial (1:1; 2:1, 500 mg, 1 g, 2 g)
80 mg/kg/day (1:1) q 6–12h;
For serious infection: 160 mg/kg/day (2:1) divided 6–12 h
NOT recommended in meningitis

Cefotaxime Sodium
Intravenous/intramuscular; Vial (250, 500 mg, 1 g)
100–150 mg/kg/day q 6–8 h

For meningitis 200 mg/kg/day q 6 h IV

Neonate < 7 days: 100 mg/kg/day q 12 h
> 7 days: 150 mg/kg/day q 8 h.

Cefpodoxime Proxetil
Oral; Syrup (50, 100 mg); tablet (100, 200 mg)
10 mg/kg/day q12 h.

Ceftazidime
Intravenous/intramuscular; Vial (250, 500 mg, 1 g)
100–150 mg/kg/day q 8 h

Neonate < 7 days: 100 mg/kg/day q 12 h
> 7 days: 150 mg/kg/day q 8 h.

Ceftriaxone Sodium
Intravenous/intramuscular; Vial (250, 500 mg, 1 g)
50–75 mg/kg/day q 12 h for AOM
100 mg/kg/day q 12 h for meningitis.

Cefuroxime Axetil
Intravenous, oral; Vial (250, 750 mg, 1.5 g),
Syrup (125 mg/5 mL), Tablet (125, 250, 500 mg)

Intravenous 75–150 mg/kg/day q 6–8 h

Oral 20–30 mg/kg/day q 12 h.

Cephalexin
Oral; syrup (125 mg/5 mL), tablet (125, 250 mg DT), capsule (250, 500 mg)
25–100 mg/kg/day q 6–8 h.

FLUOROQUINOLONES

Ciprofloxacin
Oral, intravenous; Syrup (125 mg/5 mL), tablet (250, 500 mg), injection (200 mg/100 mL, 100 mg/50 mL)

Intravenous 10–20 mg/kg/day q 8–12 h

Oral 20–30 mg/kg/day q 8–12 h.

Gatifloxacin
Oral; Tablet (200, 400 mg)
10 mg/kg/dose OD oral.

Levofloxacin
Intravenous, oral; Tablet (250, 500 mg), injection (5 mg/mL)
10 mg/kg/dose OD oral or intravenous.

Nalidixic Acid
Oral; Tablet (125, 500 mg), suspension (300 mg/5 mL)
50–55 mg/kg/day q 6–8 h
Avoid in infants < 3 months.

Norfloxacin
Oral; Tablet (100, 200, 400 mg), suspension (100 mg/5 mL)
10–15 mg/kg/day q 12 h.

Ofloxacin
Oral, intravenous; Tablet (200, 400 mg), suspension (100 mg/5 mL), injection (200, 400 mg/100 mL)

Oral 15 mg/kg/day q 12 h

Intravenous 5–10 mg/kg/day q 12 h.

Sparfloxacin
Oral, Tablet (100, 200 mg)
4 mg/kg single dose PO/day.

MACROLIDES

Azithromycin
Oral, intravenous; Tablets (250, 500 mg), suspension (100, 20 mg/5 mL), injection (500 mg)

Otitis media, community acquired pneumonia, tonsillitis 10 mg/kg PO on day 1 followed by 5 mg/kg/day OD on days 2–5. Alternately, give 30 mg/kg single dose PO. For uncomplicated typhoid fever: 20 mg/kg PO OD × 7 days. *M. avium* complex prophylaxis: 20 mg/kg/dose PO once a week

Avoid use in infants < 6 months of age.

Clarithromycin
Oral; Tablets (250, 500 mg), syrup (125 mg/5 mL)

15 mg/kg/day q 12 h, PO

M. avium complex prophylaxis: 15 mg/kg/dose PO once a week

Avoid use in infants < 6 months age

Adjust dose in renal failure. If creatinine clearance is < 50 mL/min, decrease dose by 50% and administer drug 12–24 h.

Erythromycin
Oral, intravenous; Tablets (250, 500 mg), syrup (125 mg/5 mL), injection (1 g/vial)
30–50 mg/kg/day q 6 h, PO

Intravenous dose 5 mg/kg/dose IV infusion over 8 h with normal saline or Ringer's lactate or intermittent bolus over 20–60 min every 6–8 h.

Roxithromycin
Oral; Tablets (50, 150 mg), syrup (50 mg/5 mL)
5–8 mg/kg/day q 12 h.

PENICILLINS

Amoxicillin
Oral; Capsule (250, 500 mg), suspension (125 mg/5 mL), drops (50 mg/mL)
25–50 mg/kg/day q 8 h

Recurrent otitis media 20 mg/kg/dose HS PO.

Amoxicillin—Clavulanic Acid
Intravenous, oral; Tablet (250 mg amoxicillin with 125 mg clavulanate, 500 mg amoxicillin with 125 mg clavulanate), syrup (200 amox with 28.5 mg clavulanate/5 mL, 125 mg amox with 31.5 mg clavulanate), injection [150 mg (125 mg amox), 300 mg (250 mg amox), 600 mg (500 mg amox), 1200 mg (1000 mg amox)]

Oral 20–40 mg (amox base)/kg/day q 8–12 h

Intravenous 50–100 mg (amox base)/kg/day q 6–8 h.

Ampicillin with Sulbactam
Intravenous, oral; Vial (1 g ampicillin with 0.5 g sulbactam), Tablet (375 mg containing 250 mg ampicillin)
100–200 mg/kg/day of ampicillin q 6 h IV.

Ampicillin Sodium Trihydrate
Oral, intravenous; Capsule (250, 500 mg), syrup (125 mg/5 mL), injection (250, 500 mg)

100–200 mg/kg/day q 6 h IV or oral; 200–400 mg/kg/day q 4 h IV in meningitis

200 mg/kg/day q 6 h oral for enteric fever.

Carbenicillin
Intravenous, intramuscular; Injection (1 g, 5 g)
400–600 mg/kg/day q 4 h IV or q 6 h IM.

Cloxacillin
Oral, intravenous; Vial (500 mg), capsule (250, 500 mg), syrup (125 mg/5 mL)
50–100 mg/kg/day q 6 h IV or PO (1 h before or 2 h after meals)
200 mg/kg/day q 4 h for meningitis (maximum dose 4 g/day).

Penicillin G Aqueous
Oral, intravenous; Tablet (2 lakh, 4 lakh, 8 lakh units), vial (5 lakh, 10 lakh units)
1–2 lakh units/kg/day IV infusion q 4–6 h; *For meningitis and endocarditis* 2–3 lakh units/kg/day IM q 4 h (maximum dose 24 million U/day)

For rheumatic fever prophylaxis 2 lakh units (125 mg) BD
Administer 30 min before or 2 h after meals.

Penicillin G Benzathine
Intramuscular; Vial (1.2, 2.4 million units)

Secondary prophylaxis of rheumatic fever

< 6 years 0.6 MU IM every 21 days

> 6 years 1.2 MU IM every 21 days

To be given only after test dose; can cause severe anaphylaxis. Never give IV as it may result in cardiac arrest and death.

Penicillin V (Phenoxymethyl Penicillin)
Oral; Tablet (125, 250 mg)

Infants 62.5–125 mg/dose q 6 h; *< 5 years* 125 mg/dose q 6 h; *> 5 years* 250 mg/dose q 6 h. *For rheumatic fever prophylaxis* 250

mg BD; < 5 years 125 mg BD, > 5 years 250 mg BD
250 mg is equivalent to 4 lakh units

Piperacillin
Intravenous, intramuscular; Vial (1 g, 2 g, 4 g)
100–300 mg/kg/day q 4–6 h. Dose based on piperacillin.

Piperacillin–Tazobactam
Intravenous; Vial (4 g of Piperacilin with 500 mg of Tazobactam)
300–400 mg/kg/day q 6–8 h. Dose based on piperacillin.

Procaine Penicillin
Intramuscular; Vial (4 lakh units/ vial)
Doses are based an piperacillin component.
25,000–50,000 units/kg/day single dose IM
Neonates 50,000 units/kg/day IM.

Ticarcillin Disodium
Intravenous, intramuscular; Vial (1 g, 3 g, 5 g)
200–300 mg/kg/day q 4–6 h.

MISCELLANEOUS ANTIBIOTICS

Chloramphenicol
Oral, intravenous; Capsule (250 mg, 500 mg), suspension (125 mg/5 mL), injection (1 g, 2 g vials)
50–75 mg/kg/day q 8 h PO
100 mg/kg/day q 6 h IV.

Clindamycin Hydrochloride
Oral, intravenous; Capsule (150,300 mg), injection (150 mg/mL)
Oral: 20–30 mg/kg/d div 6–8 h
IV: 20–40 mg/kg/d q 6–8 h.

Colistin Sulfate
Oral; Suspension (25 mg/5 mL)
5–15 mg/kg/day q 6–8 h.

Colistimethate Sodium (Colistin)
Intravenous, intramuscular
2.5–5 mg/kg/day q 6–12 h IV of colistin base (1 mg of colistin base = 2.67 colistemethate sodium = 33,333 IU of colistemethate sodium)
For treating ventriculitis in neonates it may additionally be given intrathecally or intraventricularly as 2000 IU/kg/day.

Doxycycline
Oral; Tablet (100 mg, 200 mg), syrup (25 mg, 50 mg/5 mL)
5 mg/kg/day q 12 h
Not recommended for children less than 8 years.

Imipenem–Cilastatin
Intravenous, intramuscular; Vials (250 mg, 500 mg)
60–100 mg/kg/day q 6 h
It is the drug of choice for extended spectrum bata-lactamase producing microorganisms (ESBL).

Linezolid
Oral, tablet (300 mg, 600 mg), injection (600 mg/300 mL)
10 mg/kg/dose q 12 h PO.

Meropenem
Intravenous, vials (500 mg, 1000 mg)

Sepsis 60 mg/kg/day q 8 h

Meningitis 120 mg/kg/day q 8 h

For neonatal sepsis 20 mg/kg/dose q 12 h.

Nitrofurantoin
Oral; Tablet (50 mg, 100 mg), syrup (25 mg/5 mL)
5–7 mg/kg/day q 6–8 h, with meals, PO

Prophylaxis for UTI 1–2 mg/kg/day HS
Avoid in G6PD deficiency.

Polymyxin
Oral, intravenous; Injection (500,000 IU per vial, 1 mg = 10,000 IU)
5–15 mg/kg/day q 8 h PO for enteric infections; 1.5–2.5 mg/kg/day q 12 h IV for systemic infections; 4 mg/kg/day q 8 h IV for meningitis/ventriculitis. For ventriculitis in neonates polymyxin may be additionally administered intrathecally or intraventricularly in a dose of 40,000 IU on alternate days for 7 days OR 20,000 IU once daily for 3 days followed by 25,000 IU on alternate days.

Teicoplanin
Intravenous; Vial (200 mg, 400 mg)
10 mg/kg/dose q 12 h for 3 doses followed by 10 mg/kg/dose 24 h.

Trimethoprim–Sulfamethoxazole
Oral, Intravenous; Syrup (trimethoprim 40 mg, sulfamethoxazole 200 mg/5 mL), Tablet (trimethoprim 20 mg/80 mg sulfamethoxazole 100 mg/400 mg)
5–8 mg/kg/day of trimethoprim q 12 h.
20-50 mg/kg/d of sulfamethoxazole q 12 h.
For Typhoid fever: 10 mg/kg/d q 12 h of Trimethoprim
For *Pneumocystis carini* pneumonia *20 mg*/kg/d q 6-8h of Trimethoprim.

Vancomycin Hydrochloride
Intravenous, oral; Vials (500 mg, 1 g), capsule (125 mg)

Sepsis 10 mg/kg/dose q 6 h IV infusion

Meningitis 15 mg/kg/dose q 6 h IV infusion

For pseudomembranous enterocolitis: 40–50 mg/kg/day q 6–8 h PO.

ANTICOAGULANTS

Low Molecular Weight Heparin (Enoxaparin)
Subcutaneous Injection (40 mg/0.4 mL, 30 mg/0.3 mL)

DVT treatment Infants 1.5 mg/kg q 12 h SC; Children and adults: 1 mg/kg q 12 h SC

Monitoring based on antifactor Xa assay, therapeutic range 0.3–0.7 U/mL.

Heparin Sodium (Unfractionated)
Injection; vial (5000 U/5 mL); 120 U = approx 1 mg.

Dose for *anticoagulation* in infants and children: Initial: 50 U/kg bolus; Maintenance: 10–25 U/kg/h as IV infusion or 50–100 U/kg/dose q 4 h IV. ECMO: 50 U/kg intravenous bolus loading; 15–35 U/kg/h intravenous infusion. *Heparin flush*: Peripheral IV: 1–2 mL of 10 U/mL solution q 4 h; Central line: 2–3 mL of 100 U/mL solution q 24 h; TPN and arterial line: Add heparin to make final concentration of 0.5–1 U/mL

Monitoring based on APTT, therapeutic range 1.5–2.5 times normal. APPT is best measured 6–8 h after initiation of changes in solution

Antidote Protamine sulfate (1 mg per 100 U heparin in previous 4 h).

Warfarin
Oral, tablet (1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg)

Initial dose 0.2 mg/kg PO × 2 days, maximum 10 mg/dose

In liver dysfunction 0.1 mg/kg/dose PO × 2 days

Maintenance Children: 0.1 mg/kg/24 h, Infants: 0.3 mg/kg/24 h Monitoring based on prothrombin time, therapeutic range 1.5–2 times normal.

ANTICONVULSANTS

ACTH
Indicated in infantile spasm and west syndrome
Intramuscular, subcutaneous; vial (25, 40 units/mL), gel (40, 80 U/mL)
20–40 units SC/IM daily for 4 weeks tapered over next 2 weeks.

Carbamazepine
Indicated in partial, tonic-clonic, atonic, akinetic epilepsy, mesial temporal lobe epilepsy syndrome, trigeminal neuralgia, post–herpetic neuralgia

Oral Tablet (200, 400 mg), syrup (100 mg/5 mL)
10–30 mg/kg/day q 8 h, PO. Initiate therapy at 30–50% of initial dose and increase over 5–7 days

Clobazam
As an add on drug in complex partial, generalized tonic-clonic, generalized tonic, absence, myoclonic, atonic and Lennox-Gastaut syndrome
Oral; tablet (5, 10, 20 mg)
0.3–1 mg/kg/day HS or divided in two doses. Avoid in children below 3 years.

For febrile seizure prophylaxis 0.5 mg/kg/dose 12 h for 48 h.

Clonazepam
Indicated in atonic, akinetic epilepsy, resistant absence attacks, myoclonic seizures, infantile spasms and Lennox–Gastaut syndrome
Oral; Tablet (0.25, 0.5, 1, 2 mg)
Initial: 0.01–0.03 mg/kg/24 h q 8–12 h, increase by 0.25–0.5 mg/24 h every 3–5 days to a maximum of 0.2 mg/kg/day
Therapeutic levels 20–80 ng/mL

Caution Tachyphylaxis.

Diazepam
For status epilepticus, to abort acute seizure, muscle relaxation in tetanus, antianxiety, sedation.
Oral, intravenous, rectal; Tablet (2.5, 5 mg), syrup (2 mg/5 mL), ampoule (5 mg/mL)

For status epilepticus Intravenous: 0.2–0.5 mg/kg/dose, repeat at 3–5 min if needed (for 2–3 doses); maximum total dose < 5 year: 5 mg, > 5 year: 10 mg; Per–rectal: 0.3–0.5 mg/kg/dose

For antianxiety, sedation, and muscle relaxation Oral 0.1–0.3 mg/kg/day q 4–8 h adjusted according to clinical response

For neonatal tetanus: 0.5–5 mg/kg/dose IV q 2–4 h
Antidote Flumazenil can revert sedation but not respiratory depression. 0.01 mg/kg IV (maximum 0.2 mg), then 0.005–0.01 mg/kg/min; maximum cumulative dose: 1 mg; may repeat after 20 min; maximum 3 mg/h.

Ethosuximide
Indicated in absence attacks
Oral, tablet (250 mg), syrup (250 mg/5 mL)

15 mg/kg/day q 12 h. Increase the dose every week till control of seizures, maintenance dose 20–40 mg/kg/day q 12 h, maximum dose ≤ 6 years: 500 mg/day and > 6 years: 1500 mg/day.

Fosphenytoin
Indicated as substitute for oral phenytoin where intravenous phenytoin is not available/possible. Used in seizures occurring during neurosurgery, status epilepticus
Intravenous; Vial (50 mgPE/mL)

Loading 15–20 mg/kg PE (not to exceed 3 mgPE/kg/min)

Maintainence dose 4–6 mg PE/kg/d IV/IM
1.5 mg fosphenytoin = 1 mg phenytoin
1 mg phenytoin = 1 mg phenytoin equivalent (PE).

Gabapentin
Add on therapy for partial seizures.
Oral; Capsules (300, 400 mg)

15–35 mg/kg/day q 8 h. Can increase over several days to 50 mg/kg/day.

Lamotrigine
Indicated in partial seizures, generalized seizures, atypical absence, atonic generalized, tonic-clonic seizures.

Oral; Tablet (5, 25, 50, 100 mg)

Started in low dose to lessen incidence of rash. Start at 0.6 mg/kg/day q 12–24 h for initial 2 weeks, followed by 1.2 mg/kg/day the next for 2 weeks followed by 5–15 mg/kg/day q 12 h. Maximum dose: 15 mg/kg/day or 400 mg/day

Caution Dose should be 1/4th in patients taking valproate

Lorazepam
Indicated in uncontrolled status epilepticus, anxiety and insomnia
Duration of action is longer than Diazepam
Oral, intravenous, intramuscular, per rectal; Tablet (1 mg, 2 mg), ampoule (2 mg/mL, 10 mg/mL)

Status epilepticus 0.05–0.2 mg/kg/dose (maximum 4 mg) over 2–5 min IV or per rectal, may repeat after 10–15 min.

Midazolam
For status epilepticus, sedation during mechanical ventilation
Intravenous, intramuscular, buccal; Vial (1 mg/mL in 5 mL and 10 mL vials, 5 mg/mL in 1 mL ampoule)
For status epilepticus 0.2 mg/kg IV or IM bolus followed by 0.1–0.2 mg/kg/h

For sedation Newborn: 0.05–0.15 mg/kg q 1–2 h; OR 0.15–0.5 µg/kg/min as continuous infusion

Children 0.05–0.2 mg/kg/dose q 1–2 h; OR 1–2 µg/kg/min as continuous infusion

Status epilepticus 0.15 mg/kg loading followed by continuous infusion of 1 µg/kg/min.

Oxcarbazepine
For partial and generalized tonic-clonic seizures.
Oral; Tablet (150, 300, 600 mg), syrup (300 mg/5 mL)

Start at 8–10 mg/kg/day q 12 h; increase to 30–45 mg/kg/day (maximum 1800 mg/day) over next 2 weeks, usual increments of 10 mg/kg/week.

Paraldehyde
For uncontrolled status epilepticus

Injection, per rectal; ampoule (5 mL, 1 g/mL)

0.1–0.2 mL/kg/dose deep IM, 0.3 mg/kg/dose PR mixed 3:1 with coconut oil. Additional dosing may be done after 30 min and then every 4–6 h.

Phenobarbitone Sodium
Indicated for neonatal seizures, tonic-clonic, akinetic, and partial seizures. May be used in febrile seizures

Intravenous, oral; Syrup (20 mg/5 mL), tablets (30, 60 mg), ampoule (200 mg/mL)

Loading dose 15–20 mg/kg IV over 15–20 min @ 1 mg/kg/min as slow IV bolus. May administer additional bolus 5 mg/kg/dose every 15–30 min up to a maximum of 30 mg/kg

Maintenance dose PO, IV

Neonates 3–5 mg/kg/day q 12 h

Infants 5–6 mg/kg/day q 12–24 h

Children 1–5 years 6–8 mg/kg/day q 12–24 h

Children 5–12 years 4–6 mg/kg/day q 12–24 h

Children > 12 years 1–3 mg/kg/day q 12–24 h

Therapeutic levels: 15–40 µg/mL. Half life varies with age: neonates 45–100 h, infants 20–133 h, children 37–73 h

Contraindication Porphyria, severe respiratory disease with dyspnea or obstruction. Use with caution in hepatic or renal disease.

Phenytoin Sodium
For tonic-clonic, atonic, akinetic, partial epilepsy.
Intravenous, oral; Tablet (50 mg, 100 mg), syrup (30 mg/5 mL), suspension (125 mg/5 mL), injection (25 mg/mL, 2 mL)

Loading dose 15–20 mg/kg slow IV @ 1 mg/kg/min. IV dose should be diluted in normal saline and not dextrose, given slowly under cardiac monitoring

Maintenance dose Neonates: 5 mg/kg/24 h q 8–12 h, children: 5–8 mg/kg/24 h divided 12–24 h

Contraindication Porphyria and heart block.

Prednisolone
For infantile spasms
2 mg/kg/day q 12 h × 2–6 weeks, taper over the next 4–12 weeks.

Pyridoxine
For pyridoxine dependent seizures
Intravenous, intramuscular, oral; Tablet (25, 50, 100 mg); Injection (100 mg/mL)
Loading 50–100 mg PO/IV followed by 50–100 mg/24 h PO

Drug induced neuritis 1 mg/kg/24 h daily

Dietary deficiency 5–15 mg/24 h for 3–4 weeks then half dose daily
Large intravenous doses can cause seizure.

Thiopental
Indicated in uncontrolled status epilepticus
Intravenous, injection (250, 500 mg, 1 g)

Loading dose 5–10 mg/kg IV over 2–5 min followed by 2–10 mg/kg/h continuous drip for uncontrolled status epilepticus. Patient to be mechanically ventilated.

Topiramate
As add on therapy for refractory partial seizures, primary generalized tonic clonic, absence seizures, Lennox–Gastaut syndrome

Oral; Tablet (25, 50, 100 mg)
1–3 mg/kg/24 h oral HS; increase by 1–3 mg/kg/day q 12 h in next 1–2 weeks till 5–10 mg/kg/day.

Valproate Sodium
Indicated in almost all types of epilepsies (broad-spectrum ACT)
Oral, intravenous; Tablet (200, 500 mg), syrup (200 mg/5 mL); Injection (100 mg/mL)
Initial dose 10–15 mg/kg/day q 8–12 h; increase by 5–10 mg/kg every week up to maximum 60 mg/kg/day

Therapeutic levels 50–100 μg/mL
Risk of hepatic failure in children < 2 years.

Vigabatrin
Indicated in resistant partial seizures, infantile spasms due to tuberous sclerosis and Lennox-Gastaut syndrome
Oral; Tablet (500 mg)
20–40 mg/kg/day, maintenance 80–100 mg/kg/day q 8–12 h.

ANTIEMETICS

Chlorpromazine
Oral, injection; Tablet (10, 25, 50, 100 mg), extended-release capsules (30, 75, 150, 200, 300 mg), syrup (10 mg/5 mL), suppository (25, 100 mg), injection (25 mg/mL)

IM or IV 2.5–4 mg/kg/day q 6–8 h (Maximum dose: < 5 years: 40 mg/24 h, 5–12 years: 75 mg/24 h)

PO 2.5–6 mg/kg/day q 4–6 h

PR 1 mg/kg/dose q 6–8 h

Adverse effects include drowsiness, jaundice, lowered seizure threshold, extrapyramidal/anticholinergic symptoms, hypotension, arrhythmias, neuroleptic malignant syndrome, bone marrow suppression.

Dimenhydrinate
Oral, injection (intravenous, intramuscular); Tablet (50 mg), injection (50 mg/mL)

Up to 12 years 5 mg/kg/day q 6–8 h PO/IV/IM (maximum dose: 2–6 years: 75 mg/day, 6–12 years: 150 mg/day)

Causes drowsiness and anticholinergic side effects. Not recommended in children < 2 years. Use recommended in management of prolonged vomiting of known etiology.

Domperidone
Oral; Tablet (10 mg), syrup (5 mg/5 mL)
0.2–0.4 mg/kg/dose 6–8 hourly
Can cause gynecomastia in males and galactorrhea in females.

Granisetron
Intravenous, oral; Tablets (1 mg), injection (1 mg/mL)
For chemotherapy induced nausea and vomiting (CINV):

Children ≥ 2 years and adults 10–20 mcg/kg/dose IV over 15–60 min before chemotherapy; may repeat 2–3 times after chemotherapy. Alternately, single dose of 40 mcg/kg/dose 15–60 min before starting chemotherapy

PO in adults 1 mg BD or 2 mg OD, started 1 h prior to chemotherapy.

Metoclopramide Hydrochloride
Oral, intravenous; Tablet (10 mg), syrup (5 mg/5 mL), ampoule (5 mg/mL)
For GER or GI dysmotility:

Neonates: 0.03–0.1 mg/kg/dose 8 hourly; Children: 0.1–0.2 mg/kg/dose 8 hourly.
Antiemetic effect:
1–2 mg/kg/dose q 2–6 h IV/IM/PO. Premedicate with diphenhydramine to reduce extrapyramidal side effects

For CINV 2–3 mg/kg/dose before and after chemotherapy.

Ondansetron Hydrochloride
Oral, intravenous, intramuscular; Tablet (4, 8 mg), syrup (4 mg/5 mL), ampoule (2 mg/mL)

IV 0.15 mg/kg/dose q 6–8 h

PO 0.1–0.2 mg/kg/dose q 6–8 h

For CINV 0.15–0.45 mg/kg/dose at 30 min before and 4 and 8 h after emetogenic drugs

Side effects include bronchospasm, tachycardia, hypokalemia, seizures, constipation or diarrhea, transient increase in liver enzymes. Avoid in QT syndrome.

Prochlorperazine
Oral, intramuscular; Tablets (5, 25 mg), injection (12.5 mg/mL)
For > 2 years old or body weight > 10 kg
0.4 mg/kg/day q 6–8 h oral. IM dose is half
Extrapyramidal symptoms or orthostatic hypotension can occur.

Promethazine Hydrochloride
Oral, IV, IM, PR; Tablet (10, 25 mg), elixir (5 mg/5 mL), ampoule (2 mL, 50 mg)
Motion sickness 0.5 mg/kg/dose q 12 h PO; First dose 30 min before starting
Sedation/antiemetic 0.25–1 mg/kg/dose q 4–6 h, PO, IM, IV or PR.

ANTIHELMINTHICS

Albendazole
Oral; Syrup (200 mg/5 mL), tablet (200 mg, 400 mg).

For pinworms, roundworms, or hookworms a single oral dose of 200 mg in children aged 1–2 years and single oral dose of 400 mg in children > 2 years; to be repeated after 2 weeks for roundworms; *Strongyloidosis*, *H. nana* infection and *Taeniasis:* 400 mg OD for 3 days; *Giardiasis:* 400 mg OD for 5 days; *Trichinosis:* 400 mg OD for 5 days; *Neurocysticercosis:* 15 mg/kg/d for 2–4 weeks with corticosteroids for 5 days to reduce edema. Albendazole is started on day 3 of steroids; *Hydatid cyst:* 400 mg BD for 4 weeks, to be taken with fatty meals. A total of 3 cycles repeated every 14 days for eradication of hydatid cysts

Albendazole is contraindicated in ocular and intraventricular cysticercosis.

Diethylcarbamazine
Oral; Tablet (50 mg, 100 mg), syrup (120 mg/5 mL)

Filariasis 6 mg/kg/day q 8h, oral, for 3–4 weeks; repeat course after 6 months; Tropical pulmonary eosinophilia and visceral larva migrans: 10 mg/kg/day, 8 h, oral for 4 weeks; Loeffler pneumonia: 15 mg/kg/day, single daily dose, for 4 days.

Ivermectin
Oral; Tablet (6 mg)

Cutaneous larva migrans, *scabies:* 0.2 mg/kg, single oral dose; *Strongyloidiasis* 0.2 mg/kg PO for 2 days; *Onchocerciasis:* 0.15 mg/kg oral single dose

Adverse effects like diarrhea, nausea, vomiting, pruritis, dizziness, drowsiness.

Levamisole

Oral; Tablet (50 mg, 150 mg), syrup (50 mg/5 mL)

Ascariasis 2 mg/kg/day PO single dose; *Hookworm infestation:* 50 mg q 6 h (4 doses); repeat course after 7 days.

Mebendazole

Oral; Tablet (100); suspension (100 mg/5 mL)

Ascariasis 100 mg twice a day × 3 days; *Enterobius infection:* 100 mg single dose, repeat after 2 weeks; *Tapeworms and mixed infections:* 200 mg BD × 3 days; repeat course after 2–4 weeks; *Hydatid cyst:* 30 mg/kg/day q 8 h, oral, for 4 weeks

Not recommended in children below 2 years. Should be taken with food.

Niclosamide

Oral; Tablet (500 mg).

For *Taenia saginata, Taenia solium, Diphyllobothrium latum* and *H. nana*: 1 g empty stomach followed by another dose after 1 hour. A brisk purgative is given after 2 hours of last dose. For Dwarf tapeworm, single dose as above followed by half dose for the next 6 days. Use half of this dose in children < 6 years.

Nitazoxanide

Oral; Tablet (100 mg, 500 mg); syrup 100 mg/5 mL
For ascariasis, Dwarf tape worm: 2 to 3 years: 100 mg BD × 3 d, *4 to 11 years:* 200 mg BD × 3 days, *>12 years:* 500 mg BD × 3 d.

Piperazine

Oral; Tablet (500 mg), elixir (750 mg/5 mL)
Ascariasis: 75 mg/kg/day PO single dose on two consecutive nights (maximum dose 3.5 g/d)
Enterobius: 65 mg/kg/day PO single dose × 7 days (maximum dose 2.5 g/d).

Praziquantel

Oral; Tablet (500 mg, 600 mg)

Neurocysticercosis 50 mg/kg/day q 8 h, oral × 15 day with steroids to counter the raised intracranial tension; *Tapeworm:* 5–10 mg/kg, single dose; *Schistosomiasis:* 20 mg/kg/dose PO 8–12 hourly × 1 day; *Liverfluke:* 25 mg/kg/dose q 8 h × 2 days. *H. nana:* 25 mg/kg PO single dose.

Contraindication Ocular and intraventricular cysticercosis.

Pyrantel Pamoate

Oral; Tablet (250 mg), suspension (250 mg/5 mL)
11 mg/kg single dose (maximum 1 g), repeat after 2 weeks; *Hookworm:* 11 mg/kg/dose, once daily × 3 days
Avoid in liver disease.

Thiabendazole

Oral; Tablet (500 mg), suspension (500 mg/5 mL)
50 mg/kg/day q12 h (max: 3 g/day); Duration of therapy for *Strongyloides, intestinal nematodes:* 2 days; *visceral larva migrans:* 5–7 days; Trichinosis: 2–4 days, cutaneous larva migrans: 2–5 days.

ANTIHISTAMINICS

Astemizole

Oral; Tablet (10 mg), syrup (5 mg/5 mL)

< 6 years 0.2 mg/kg OD

6–12 years 5 mg OD

> 12 years 10 mg OD.

Caution Can cause QT prolongation and life-threatening arrhythmias if given with drugs like erythromycin, itraconazole, ketoconazole, cimetidine, ciprofloxacin. Avoid abrupt discontinuation. It has a long elimination half-life and is less sedating. Avoid in liver disease.

Cetirizine Dihydrochloride

Oral; Tablet (5 mg, 10 mg), syrup (5 mg/5 mL)
Caution: Avoid in children < 2 years
2–6 years: 2.5 mg BD or 5 mg OD
> 6 years: 5 to 10 mg OD.

Chlorpheniramine Maleate

Oral, parenteral (IV/IM/SC); Tablet (2, 4 mg), syrup (2 mg/5 mL), injection (10 mg/mL)

Children 0.35 mg/kg/day PO q 4–6 h or dose based on age bands as below:

2–6 years 1 mg/dose PO q 4–6 h, max 6 mg/24 h

6–12 years 2 mg/dose PO q 4–6 h, max 12 mg/24 h

≥ 12 years 4 mg/dose q PO 4–6 h, max 24 mg/24 h

IV/IM/SC 5–20 mg once, max 40 mg/24 h.

Cyproheptadine Hydrochloride

Oral; Tablet (2 mg, 4 mg), syrup (2 mg/5mL)

Children 0.25–0.5 mg/kg/day q 8–12 h

2–6 years 2 mg q 8–12 h (max 12 mg/day)

> 6 years 4 mg q 8–12 h (max 16 mg/day)

Contraindication Neonates and children suffering from asthma, glaucoma, or GI/GU obstruction, and therapy with MAO inhibitors.

Desloratadine

Oral; Tablet (5 mg)

2–5 years 1 mg OD

6–12 years 2.5 mg OD.

Diphenhydramine Hydrochloride

Oral, intravenous; Tablet (25 mg, 50 mg), syrup (12.5 mg/5 mL), injection (50 mg/mL, 10 mg/mL)
1 mg/kg/dose PO q 6 h, max 300 mg/day

Phenothiazine toxicity 1 mg/kg intravenous.

Fexofenadine Hydrochloride

Oral; Tablet (30 mg, 120 mg, 180 mg), syrup (30 mg/5 mL)

6 months–2 years 15 mg BD

2–12 years 30 mg BD

> 12 years 60 mg BD or 120 mg OD.

Hydroxyzine Hydrochloride

Oral, intramuscular; Tablet (10 mg, 25 mg), syrup (10 mg/5 mL), injection (25 mg/mL)
0.6 mg/kg/dose q 6 h PO
0.5–1 mg/kg/dose q 6 h intramuscular.

Loratadine

Oral; Tablet (5 mg, 10 mg), syrup (5 mg/5mL)

< 30 kg 5 mg/24 h

> 30 kg 10 mg/24 h

Pheniramine Maleate

Oral, intramuscular, intravenous; Tablet (25 mg, 50 mg), syrup (15 mg/mL), injection (22.75 mg/mL)
0.5 mg/kg/day q 8 h PO, IM or IV.

Promethazine Hydrochloride

Oral, intramuscular, intravenous; Tablet (10 mg, 25 mg), syrup (5 mg/mL), injection (25 mg/mL)

Allergy 0.1 mg/kg/dose q 6–8 h PO/IM;

Sedation 1–2 mg/kg/single dose PO/IM;

Nausea–vomiting 1 mg/kg/day q 6 h PO/IM.

Pseudoephedrine

Oral; Tablet (60 mg), syrup (30 mg/5 mL)
4 mg/kg/day q 6–12 h PO.

ANTIHYPERTENSIVES

Amiloride

Potassium sparing diuretic; rarely used alone because of risk of hyperkalemia, mild antihypertensive activity, used concomitantly with a thiazide diuretic.
Oral; Tablet (2.5, 5 mg)
0.4–0.625 mg/kg/day q 12–24 h

Caution Do not use in renal failure, hyperkalemia.

Amlodipine

Calcium channel blocker

Oral, Tablet (5 mg)

Starting dose 0.05 to 0.1 mg/kg/day, may increase to 0.3 to 0.4 mg/kg/day. Titration should be done slowly, at one to two week intervals given once daily.

Atenolol

Cardioselective beta–blocker
Oral; Tablet (50, 100 mg)
0.8–1.5 mg/kg/day (maximum 2 mg/kg/day)

Caution Should not be stopped suddenly, taper over 2 weeks.

Captopril

Angiotensin converting enzyme inhibitor
Oral; Tablet (12.5, 25, 50 mg)

Neonates 0.1–0.4 mg/kg/day PO q 6–24 h.

Children Initial dose: 0.3–0.5 mg/kg/dose q 8 h; titrate upward if needed; maximum 6 mg/kg/day q 8–12 h.

Use with caution in collagen vascular disease. Adjust dose in renal failure. May cause rash, proteinuria, neutropenia, angioedema, dysgeusia, hypotension and hyperkalemia.

Carvedilol

Nonselective beta blocker with alpha blocking action
Oral; Tablet (3.125, 6.25, 12.5, 25 mg)
0.05 mg/kg/dose BD, increase every 2 weeks by 0.05 mg/kg/dose for the first increment and then 0.1 mg/kg/dose over 3 months till max 0.35 mg/kg/dose BD (Maximum: 25 mg BD).

Adverse effects Hypotension, dizziness, AV block, arrhythmia.

Clonidine Hydrochloride

Central alpha-adrenergic agonist
Oral, injection, transdermal; Tablet (100, 200, 300 µg), injection (100 µg/mL), transdermal patch (0.1, 0.2, 0.3 mg/24 h × 7 days)
1–2 µg/kg/dose q 6 h; maximum 25 µg/kg/day.

Adverse effects Dry mouth, dizziness, drowsiness, constipation, fatigue.
Do not discontinue abruptly, taper gradually over 1 week.

Diazoxide

Potassium channel activator
Injection, oral; Ampoule (15 mg/mL), syrup (50 mg/mL), capsule (50 mg).

Hypertensive crisis 1–3 mg/kg/dose IV up to maximum of 150 mg/dose, repeat q 5–15 min, then q 4–24 h.

Hyperinsulinemic hypoglycemia < 1 year: 8–15 mg/kg/24 h q8–12 h, > 1 year: 3–8 mg/kg/day q 8–12 h.

Adverse effects include hyponatremia, salt and water retention, GI disturbances, rash, ketoacidosis, hypertrichosis, arrhythmias.

Enalapril Maleate

Angiotensin converting enzyme inhibitor
Oral; Tablet (2.5, 5 mg)

Oral 0.1–0.5 mg/kg/day q 12–24 h

Intravenous 0.005–0.01 mg/kg/dose q 8–24 h.

Contraindication Bilateral renal artery stenosis
Side effects include nausea, diarrhea, headache, dizziness, hyperkalemia, hypoglycemia, hypersensitivity, vough and hypotension.

Esmolol Hydrochloride

Beta-1 selective adrenergic blocker
Intravenous; injection (10, 250 mg/mL)
Loading: 100–500 µg/kg IV over 1 min
Maintainence dose 25–100 µg/kg/min infusion, may increase rate every 10 mins by 25–50 µg/kg/min up to 500 µg/kg/min

Hydralazine Hydrochloride

Arterial vasodilator
Oral, injection; Tablet (10, 25, 50, 100 mg), Oral liquid (1.25, 2, 4 mg/mL), ampoule (20 mg/mL).

Hypertensive crisis 0.1–0.2 mg/kg/dose IM or IV q 4–6 h, maximum 20 mg/dose.

Chronic hypertension Start at 0.75–1 mg/kg/day PO q 6–12 h (Maximum 25 mg/dose). Can increase if needed to 5 mg/kg/day for infants and 7.5 mg/kg/day for older children.

Use with caution in severe renal and cardiac disease.

Labetalol

Adrenergic agonist (alpha and beta)
Oral, intravenous; Tablet (50, 100 mg), ampoule (5 mg/mL), suspension (10 mg/mL)

Oral 2 mg/kg/dose 12 hly; Maximum dose 40 mg/kg/d

Hypertensive emergency IV 0.2–1 mg/kg/dose q 10 min; Infusion: 0.4–1 mg/kg/h to maximum of 3 mg/kg/h; can initiate with 0.2–1 mg/kg bolus, maximum 20 mg bolus.

Contraindications Asthma, heart block, cardiogenic shock, pulmonary edema.

Methyldopa

Alpha–2 receptor agonist
Oral, intravenous; Tablet (250 mg), injection (50 mg/mL)

Hypertension 5–40 mg/kg/day PO q 6–8 h.

Hypertensive crisis 2–4 mg/kg/dose IV to maximum of 5–10 mg/kg/dose IV 6–8 h.

Contraindications Liver disease, pheochromocytoma, and depression.

Side effects include positive Coombs test, GI disturbance, memory impairment, hepatitis, black tongue, orthostatic hypotension, fever, leukopenia and sedation.

Metoprolol
Beta-1 receptor blocker
Oral; Tablet (50,100 mg), injection (1 mg/mL)

Oral 1–5 mg/kg/day q 12 h; Intravenous: 0.1 mg/kg/dose

Contraindications Congestive heart failure.

Minoxidil
Direct vasodilator
Oral; Tablet (2.5, 5, 10 mg)

Starting dose 0.2 mg/kg/day PO as single dose; can be increased till 5 mg/day. Increase by 0.1–0.2 mg/kg/day at 3-day intervals. Usual effective dose: 0.25–1 mg/kg/day PO q 12–24 h. Maximum tolerated dose: 5 mg/kg/day or 50 mg/day.

Can cause dizziness, CHF, pulmonary edema, pericardial effusion, Steven-Johnson syndrome, leukopenia, and hypertrichosis (reversible).

Nifedipine
Calcium channel blocker
Oral; Capsule (5, 10, 20 mg), tablet retard (20 mg), tablet (10 mg)
For hypertensive emergency/hypertension: 0.25–0.5 mg/kg/dose q 4–6 h (maximum 10 mg/dose). 300–500 μg/kg/dose sublingual for severe hypertension.
For hypertrophic cardiomyopathy: 0.5–0.9 mg/kg/d q 6–8 h PO/SL. May cause hypotension, flushing, tachycardia, headache, dizziness and nausea.

Caution Avoid concurrent beta blockers.

For sublingual administration, capsule to be punctured and liquid expressed in mouth. Do not chew/crush sustained release tablets.

Propranolol
Adrenergic blocking agent (Beta blocker)
Tablet (10, 40, 80 mg)

Hypertension 0.5–1 mg/kg/day q 6–12 h, increase gradually if needed to a maximum 8 mg/kg/day.

Adverse effects include hypoglycemia, hypotension, nausea, vomiting, depression, weakness, bronchospasm and heart block. Avoid in bronchial asthma, heart block, congestive heart failure.

Sodium Nitroprusside
Vasodilator
Intravenous; Ampoule (50 mg/ampule)
0.5–3 μg/kg/min as intravenous infusion. 50 mg dissolved in 1 liter of 5% dextrose to provide a concentration of 50 μg/mL.

Caution Do not use in coarctation of aorta, arteriovenous shunts, raised intracranial tension, liver failure, congestive heart failure. Risk of methemoglobinemia and metabolic acidosis. Should not be used beyond 72 h.

Verapamil
Calcium channel blocker
Oral, intravenous; Tablet (40, 80, 120 mg), ampoule (2.5 mg/mL)

Oral 1–2 mg/kg/dose q 6–8 h, intravenous: 0.1–0.2 mg/kg/dose, give over 2–3 min under ECG monitoring

Antidote calcium gluconate;

Caution Avoid in neonates due to a high-risk of heart block, apnea, bradycardia and hypotension.
Do not use to treat SVT in infants.

Contraindication Hypersensitivity, cardiogenic shock, severe CHF, sick–sinus syndrome or AV block.

ANTIMALARIALS

Amodiaquine
Oral; Tablet (200 mg base), suspension (150 mg base/5 mL)
10 mg/kg of base stat PO and then 5 mg/kg at 6 h, 24 h, 48 h
Used in combination with artesunate.

Artemether
Oral, intramuscular; Tablet (20 mg, 40 mg, 80 mg; in combination with lumefantrine), injection (80 mg/mL).

For severe and complicated malaria 3.2 mg/kg IM on day 1 followed by 1.6 mg/kg daily for the next 6 days

For treatment of uncomplicated *P falciparum* malaria

The oral dose for fixed dose combination therapy (artemether 20 mg + lumefantrine 120 mg) is as followed:

5–14 kg 1 tablet BD for 3 days

15–24 kg 2 tablet BD for 3 days

25–34 kg 3 tablet BD for 3 days

> 34 kg 4 tablet BD for 3 days.

Artesunate
Intravenous, intramuscular, oral; Vial (50 mg), tablet (50 mg, 100 mg, 200 mg) as part of artesunate combination therapy.

Oral 4 mg/kg/day OD for 3 days as part of artesunate combination therapy.

For severe and complicated malaria 2.4 mg/kg IV bolus or IM (loading dose) followed by 2.4 mg/kg IV or IM at 12 h and then OD for 6 days.

For chloroquine resistant malaria
- Artesunate—4 mg/kg OD × 3 days + sulfadoxine-pyrimethamine (25/1.25 mg/kg) on day 1
- Artesunate—4 mg/kg OD × 3 days + mefloquine 25 mg/kg in two (15 +10) divided doses on day 2 and day 3 followed by single dose primaquine 0.75 mg/kg.

Chloroquine Phosphate
Oral; Tablet 250(150 mg base), syrup (50 mg/5 mL)

10 mg/kg (base) followed by 5 mg/kg (base) after 6 h, 24 h and 48 h from first dose OR

10 mg/kg (base) followed by 10 mg/kg (base) after 24 h followed by 5 mg/kg (base) after 48 h from first dose.

To repeat dose if vomiting within 30 min of intake.

Lumefantrine
Oral; Fixed dose combination with artemether (artemether 20 mg + lumefantrine 120 mg, artemether 40 mg + lumefantrine 240 mg).

Dose as mentioned under artemether.

Mefloquine Hydrochloride
Oral; Tablet (250 mg)

Used as combination therapy with artesunate as:

25 mg/kg divided as 15 mg/kg on D1 and 10 mg/kg on D2 OD

Used as single drug for prophylaxis as 3.5 mg/kg of base weekly.

Primaquine
Oral; Tablet (2.5 mg, 7.5 mg, 15 mg)

0.25 mg/kg OD for 14 days For radical cure in *P. vivax*

0.75 mg/kg single dose For gametocidal effect in *P. falciparum*
Avoid in G6PD deficiency.

Pyrimethamine–sulfadoxine
Oral; Tablet (25 mg pyrimethamine + 500 mg sulfadoxine), syrup (12.5 mg pyrimethamine+ 250 mg sulphadoxine/5 mL)
1.25 mg/kg pyrimethamine/25 mg/kg sulfadoxine as single dose with artesunate for treatment of chloroquine resistant uncomplicated *P. falciparum* malaria.

Quinine Dihydrochloride
Intravenous; Ampoule (300 mg/mL)
For treatment of severe malaria

Intravenous 20 mg/kg salt diluted in normal saline or 5% dextrose in a concentration of 1 mg/mL given as a loading dose over 4 h followed by 10 mg/kg/dose as in fusion over 4 h every 8 h for 7–10 days. Shift to oral therapy as soon as possible.

Quinine Sulfate
Oral; Tablet (150, 300 mg salt)

Oral 10 mg/kg/dose of salt every 8 h (for uncomplicated chloroquine resistant *P. falciparum* infections). Used in combination with tetracycline (40 mg/kg/day q 6 h × 10 days), or clindamycin (20–40 mg/kg/day q 8 h × 3 days) or Pyrimethamine (0.75 mg/kg/day q 12 h × 3 days), or sulfadiazine (150 mg/kg/day q 8 h × 6 days) to prevent drug resistance.

ANTIRETROVIRAL DRUGS

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine (AZT/ZDV)
Oral, intravenous; Capsules (100 mg), liquid (50 mg/5 mL), injection (10 mg/mL). Available also in combination with Lamivudine as combivir (Tablets: 300 mg AZT + 150 mg 3TC).
Daily dose 360 mg/m^2 to maximum 600 mg.

Weight-based dosing 4–9 kg: 12 mg/kg BD, 9–30 kg: 9 mg/kg BD, ≥ 30 kg: 300 mg BD.

Neonate 2 mg/kg/dose QID PO or 1.5 mg/kg/dose QID IV over 60 min. Begin within 12 hours of birth and continue until 6 weeks of age.

Side effects include anemia, neutropenia, headache, vomiting, neuropathy, anorexia, vomiting, hepatitis, lactic acidosis, myopathy.

Lamivudine (3TC)
Oral; Tablets (150 mg, 300 mg), solution (5 mg/mL, 10 mg/mL).
4 mg/kg/dose BID. Maximum 150 mg/dose. Available in fixed dose combination with lamivudine as combivir (300 mg AZT + 150 mg 3TC), or with abacavir (300 mg 3TC + 600 mg ABC), or both (150 mg 3TC + 300 mg AZT + 300 mg ABC).

Common side effects are headache, fatigue, nausea, diarrhea, skin rash, pancreatitis, abdominal pain, peripheral neuropathy, decreased neutrophil count, and increased liver enzymes.

Stavudine (d4T)
Oral; Capsules (15 mg, 20 mg, 30 mg, 40 mg), solution (1 mg/mL).
1 mg/kg/dose BID. Maximum daily dose of 80 mg.

Common side effects are headache, gastrointestinal discomfort, and rash. Peripheral neuropathy, pancreatitis, lactic acidosis, and raised liver enzymes may occur.

Didanosine (ddI)
Oral.
180 mg/m^2/day divided into two doses. Maximum daily dose 400 mg. Administer empty stomach.

Side effects include headache, diarrhea, abdominal pain, pancreatitis, nausea, vomiting, peripheral neuropathy, dyselectrolytemias, hyperuricemia, increased liver enzymes, lactic acidosis, retinal pigmentation, CNS depression, rash/pruritis, myalgia, pancreatitis.

Abacavir (ABC)
Oral; Tablets (300 mg). Oral solution (20 mg/mL).
8 mg/kg/dose BID.

Life-threatening hypersensitivity reactions have been reported presenting as fever, skin rash, fatigue and gastrointestinal symptoms (nausea, vomiting, diarrhea or abdominal pain).

Zalcitabine (ddC)
Oral.
0.01 mg/kg/dose TID.

Use cautiously in patients with liver disease, pancreatitis, or severe myelosuppression. Adjust dose in renal disease. Common side effects are peripheral neuropathy, headache, malaise, gastrointestinal disturbances.

Emtricitabine (FTC)
Oral; Solution (10 mg/mL), Capsule (200 mg).

Dose in 0–3 months 3 mg/kg OD, 3 months–17 years: 6 mg/kg OD (Maximum dose 240 mg).

Minimal toxicity. Severe hepatitis in children with hepatitis B co–infected persons.

Nucleotide Reverse Transcriptase Inhibitors
Tenofovir (TDF)
Oral; Tablet (150 mg, 200 mg, 250 mg, 300 mg).
Not recommended in children aged < 2 years.

Pediatric dose 8 mg/kg once daily.

Adverse effects Asthenia, headache, diarrhea, nausea, vomiting, flatulence, renal insufficiency, decreased bone mineral density.

Non-nucleoside Reverse Transcriptase Inhibitors

Efavirenz (EFV)
Oral; Capsules (50 mg, 100 mg, 200 mg).
15 mg/kg once a day. Maximum of 600 mg.

Usually not recommended in children < 3 years age/weight < 10 kg. Side effects include rash, granulocytopenias, hepatotoxicity and psychosis.

Nevirapine (NVP)
Oral; Tablets, syrup (10 mg/5 mL).
Start with 120 mg/m^2 once a day for initial 14 days followed by 120 mg/m^2/dose BID if no rash or other side effects. Maximum tolerated dose 400 mg/day.

For PMTCT:

Birth weight < 2 kg 2 mg/kg PO started within 24 hours of birth and given for 6 weeks of life.

Birth weight 2–2.5 kg 10 mg, PO, OD.

Birth weight ≥ 2.5 kg 15 mg, PO, OD.

Side effects include nausea, pain abdomen, skin rash (can be life-threatening Stevens-Johnson type), granulocytopenia and hepatotoxicity. Discontinue if severe rash with fever, blistering, myalgias or mucositis occur. Nevirapine induces the metabolism of CYP4503AA to cause its own metabolism within 2–4 weeks of starting treatment. NVP decreases levels of indinavir, ritonavir, and saquinavir. Rifampicin and rifabutin decrease serum levels of NVP.

NVP should be taken with food to decrease gastrointestinal irritation.

PROTEASE INHIBITORS

Nelfinavir (NFV)

Neonates 40 mg/kg/dose PO BID; Children (> 3 months): 25–30 mg/kg/dose PO TID, maximum 750 mg/dose.

Ritonavir (RTV)

Oral; Solution (80 mg/mL), tablets (100 mg) available alone or in combination with other PIs. The major use of ritonavir is as an enhancer of other protease inhibitors (PIs) used in pediatric patients and in adolescents and adults.

Adverse effects include gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, paresthesia (circumoral and extremities), hyperlipidemia, especially hypertriglyceridemia, hepatitis, asthenia, taste perversion, hyperglycemia, fat maldistribution, and rash.

The recommended dose of ritonavir varies and is specific to the drug combination selected.

Lopinavir/Ritonavir (LPVr)

Oral; Solution (80 mg/20 mg LPV/r per mL; Contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume), tablets (100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r).

Daily dose 460/115 mg/m^2 divided in 2 doses (maximum 800/200 mg per day) in ARV–naïve patients. 300 mg/75 mg per m^2 of BSA per dose twice daily (maximum dose 400 mg/100 mg twice daily). For is the preferred dose for treatment–experienced patients with possible decreased lopinavir susceptibility.

Can be administered without regard to food; administration with or after meals may enhance GI tolerability. Once–daily dosing is not recommended because of considerable variability in plasma concentrations in children aged < 18 years and higher incidence of diarrhea.

Adverse effects include diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceri-demia, fat maldistribution.

Indinavir

Not approved for use in infants. Generally avoided in children. If used, doses of 234–500 mg/m^2 BSA boosted with ritonavir have been tried.

Fasting increases absorption. *Adverse effects* include nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia, lipid abnormalities, pruritus, and rash, nephrolithiasis/urolithiasis with indinavir crystal deposits.

Saquinavir (SQV)

Generally avoided in children < 2 years. In children ≥ 2 years, dosing based on body weight and in combination with ritonavir.

5–15 kg SQV 50 mg/kg + RTV 3 mg/kg BD

15–40 kg SQV 50 mg/kg + RTV 2.5 mg/kg BD

≥ 40 kg SQV 50 mg/kg + RTV 100 mg BD.

Fatty meals increase absorption.

Atazanavir (ATV)

Oral.
Recommended in children > 6 years.
Dosing in combination with ritonavir and according to weight bands.

15–20 kg ATV 150 mg + RTV 100 mg OD with food

g ATV 200 mg + RTV 100 mg OD with food

≥ 40 kg ATV 300 mg + RTV 100 mg OD with food.

Adverse effects include jaundice, prolonged PR interval, first–degree symptomatic atrioventricular (AV) block, nephrolithiasis, hyperglycemia, fat maldistribution, rash, raised liver enzymes.

Darunavir (DRV)

Oral; Tablets (75 mg, 150 mg, 400 mg, 600 mg, 800 mg), oral suspension (100 mg/mL).

Not recommended in children < 3 years or weight < 10 kg because of risk of seizures.

Dosing according to weight band.
10–11 kg DRV 200 mg + RTV 32 mg
11–12 kg DRV 220 mg + RTV 32 mg
12–13 kg DRV 240 mg + RTV 40 mg
13–14 kg DRV 260 mg + RTV 40 mg
14–15 kg DRV 280 mg + RTV 48 mg
15–30 kg DRV 375 mg + RTV 48 mg
30–40 kg DRV 450 mg + RTV 100 mg
≥ 40 kg DRV 600 mg + RTV 100 mg.

DRV should be administered with food.

Side effects include skin rash, hepatitis, fat maldistribution, diarrhea, nausea, headache, and hyperlipidemia.

Tipranavir

Oral; Solution (100 mg/mL, with 116 International Units (IU) vitamin E/mL), capsule (250 mg).

Not approved for use in children aged < 2 years.

Dose 375 mg/m^2 plus RTV 150 mg/m^2, both twice daily.

To be administered with food.

Adverse effects include intracranial hemorrhage, skin rash, hepatitis, hyperglycemia, hyperlipidemia, fat maldistribution, nausea, vomiting and diarrhea.

ANTITOXINS AND IMMUNOGLOBULINS

Anti-Rh D Immunoglobulin

Intramuscular; Vial (100, 250, 300, 350 µg).
For antenatal prophylaxis: 300 µg single dose IM at 28 weeks and 34 weeks of gestation or within 72 hours of delivery; For abortion, amniocentesis, version: 250 µg IM.
For immune thrombocytopenic purpura 50–75 µg/kg IV single dose

Anti-Snake Venom (ASV)

Intravenous; Vial (10 mL).

Mild envenomation 5 vials, *moderate envenomation* 5–15 vials, *severe envenomation* 15–20 vials. Small children may require 1.5 times of this dose. Dilute the ASV in 250 mL of N/5 saline and given IV @20 mL/kg/hours. Sensitivity test (intradermal 0.02 mL of 1:10 diluted ASV) is necessary.

Diphtheria Antitoxin (Equine)

For Schick Test Positive Contacts
One dose of diphtheria toxoid should be given in one arm and 500–2000 U(IM) of diphtheria antitoxin in the other arm. Six weeks later, 3 doses of toxoid may be given monthly.

Therapeutic
Intravenous; Ampoule (10,000; 20,000 U)

Pharyngeal/laryngeal 20,000–40,000 U IV

Nasopharyngeal 40,000–60,000 U IV

Extensive 80,000–1,20,000 U IV.

Caution Dilute the antitoxin in 1:20 isotonic sodium chloride solution and give at rate of 1mL/min.

Human High Dose Immunoglobulin
Intravenous, vial (0.5, 1, 2, 5 g).

For prophylaxis and treatment of life–threatening gram-negative infections, immunodeficiency states, chronic ITP, Gullian-Barré syndrome, and Kawasaki disease.

400 mg/kg/day IV infusion over 6 hours × 5 days, or 1 g/kg/day IV infusion over 2 hours × 2 days, or 2 g/kg IV infusion over 10–12 hours as single dose.

Human Normal Immunoglobulin
Intravenous, intramuscular; Vial (10%, 16.5% in 1mL vial).

In primary immunodeficiency 300–400 mg/kg intravenous once every 4 weeks.

For attenuation of disease among close contacts 0.3 mL/kg of 10% solution IM within 6 days of exposure to measles; 0.02–0.04 mL/kg of 10% solution IM following exposure to hepatitis A.

Caution No live vaccines to be given in next 6 weeks.

Human Hepatitis B Immunoglobulin (HBIG)
Intramuscular, intravenous; Vial (160 mg/mL; 200 IU/mL).

Newborn 0.5 mL intramuscular up to 72 hours of birth, preferably within 12 hours of birth. Active immunization should be initiated simultaneously. The vaccine and HBIG should be administered in separate thighs.

Children 0.06 mL/kg or 40 IU/kg, single dose intramuscular.

Human Rabies Immunoglobulin
Intramuscular; Vial (150 U/mL)

20 U/kg, infiltrate in local site as much as possible, rest to be given intramuscular in gluteal region. If patient presents between 1–7 days, give the entire dose IM. Administer rabies vaccine simultaneously

Caution To be given within 24 hours of bite. Perform prior intra-dermal testing for hypersensitivity.

Human Tetanus Immunoglobulin
Intramuscular; vial (250, 500 IU).

Prophylaxis 250 IU IM, or 500 U if there is heavy contamination or > 24 hours have elapsed.

Treatment 30–300 IU/kg IM

Intrathecal 250–500 IU single dose.

Respiratory Syncytial Virus (RSV) IG
Intravenous; Vial (50 mg/mL).

For infants and children < 2 years with bronchopulmonary dysplasia (BPD) who require oxygen, initiate RSV IG within 6 months before RSV season. May administer prophylactically in preterm infants (< 32 weeks) who do not have BPD. For those ≤ 28 weeks, consider till 12 months of age and for those with gestational age 29–32 weeks, may give RSV IG until 6 months of age.
Dose 750 mg/kg IV every 30 days.

Contraindication Cyanotic congenital heart disease.

Varicella Zoster Immunoglobulin (VZIG)
Intramuscular; Vial (125 U per vial).

125 U for each 10 kg body weight IM, max 625 U, min 125 U. Give IM within 48 hours or at least 96 hours of exposure.

Indications Neonates of mother developing varicella 5 days before to 2 days after pregnancy, postnatally exposed preterm infants (≥ 28 weeks) of susceptible mothers, hospitalized preterm infant born at < 28 weeks' gestation or birth weight < 1 kg, immunocompromised children, susceptible pregnant women.

ANTIVIRAL DRUGS

Acyclovir
Oral, intravenous; Tablet (200, 400, 800 mg), suspension (400 mg/5 mL), injection (250 mg).

Intravenous 10 mg/kg/dose q 8 h (to give for 14 days for HSV encephalitis).

Oral 20 mg/kg/dose q 6 h (to give for 5 days for varicella).

Amantadine Hydrochloride
Oral; Capsule (100 mg), syrup (50 mg/5 mL).
2–4 mg/kg/dose q 12 h.
Maximum dose < 10 years: 150 mg/d, > 10 years: 200 mg/d

Foscarnet
Intravenous; injection (500 mg, 1g).
CMV retinitis in AIDS 60 mg/kg/dose q 8 h as slow IV infusion during induction phase followed by 90 mg/kg/dose OD IV infusion during maintenance phase.

Ganciclovir
Oral, intravenous; Capsule (250 mg, injection (500 mg).
5 mg/kg/dose 12 hourly during induction phase followed by 5 mg/kg/dose OD during maintenance phase of treatment of CMV retinitis in immunocompromised host.

For severe infections: 10 mg/kg/dose q 8 h IV for 14 days.

Isoprinosine
Oral; Intramuscular; Tablet (500 mg)
50–100 mg/kg/d q 12 h PO/IM.

Oseltamivir
Oral; Capsule (30 mg, 45 mg, 75 mg), syrup (12 mg/mL).
< 3 months: 12 mg BD; < 15 kg: 30 mg BD; 15–23 kg: 45 mg BD; 23–40 kg: 60 mg BD; > 40 kg: 75 mg BD. For 5 days duration.

Ribavirin
Oral; Capsule (100 mg, 200 mg), syrup (50 mg/5 mL).
10 mg/kg/day PO q 6–8 h.

CARDIOTONICS

Adrenaline (Epinephrine Hydrochloride)
Intravenous, subcutaneous, endotracheal; Ampoule (1:1000; 1 mg/mL), dilute in normal saline.

For cardiac arrest 0.1 mL/kg of 1:10,000 diluted intravenous or intratracheal q 3-5 min.

For resuscitation in neonates, use 1:10,000 dilution 0.1–0.3 mL/kg IV q3–5 min or 0.3–0.5 mL/kg ET.

For CPR in older children, use 1:1000 dilution 0.1 mg/kg IV/ET q 3–5 min.

For shock 0.05-0.5 µg/kg/min IV infusion.

For bronchodilation: 1:1000 dilution, 0.01 mg/kg/dose SC, q 15 min × 3–4 doses.

For nebulization 0.5 mL/kg of 1:1000 solution diluted in 3 mL normal saline (Max dose in ≤ 4 years: 2.5 mL/dose and in older children: 5 mL/dose).

Amrinone
Intravenous; Injection (100 mg/20 mL).
0.75 mg/kg IV bolus over 2–3 min followed by 3–5 µg/kg/min in newborns and 5–10 µg/kg/min in children as continuous infusion.

Digoxin
Intravenous, oral; Injection (0.5 mg/2 mL), tablet (0.25 mg), elixir (0.5 mg/mL).

Digitalizing dose (oral) Preterm neonates: 0.04 mg/kg/day; Term neonates: 0.06 mg/kg/day; < 2 years: 0.04–0.05 mg/kg/day; > 2 years: 0.04 mg/kg/day; Parenteral dose: 2/3rds of oral dose – ½ of digitalizing dose given stat, 1/4th after 8 hours and 1/4th after 16 hours

Daily maintenance dose 1/4th of digitalizing dose.

Dobutamine
Intravenous; Vial (1 mL = 50 mg, 5 mL).
5–20 µg/kg/min IV infusion.
Do not mix with sodium bicarbonate.

Dopamine
Intravenous; Ampoule (1 mL=40 mg, 5 mL).
5–20 µg/kg/min.
Do not mix with sodium bicarbonate.

Milirinone
Intravenous; Injection (1 mg/mL).

Loading dose 50 µg/kg

Continuous infusion 0.25–1 µg/kg/min.

Norepinephrine
Intravenous; Ampoule (1 mg/mL).
0.05–0.1 µg/kg/min. Maximum dose 2 mg/kg/min. To be given by central line only. Extravasation causes severe tissue necrosis.

Vasopressin
Intravenous, subcutaneous; Ampoule (20 U/mL)

Diabetes insipidus 2.5–10 U/dose q 6–12 h subcutaneous

Bleeding esophageal varices 0.002–0.01 U/kg/min continuous infusion

Catecholamine refractory shock 0.3–2 U/kg/min.

DIURETICS

Acetazolamide
Oral; Tablet (250 mg).
5 mg/kg/dose q 8 h as diuretic; 50–70 mg/kg/day q 8 h for raised intracranial pressure.

Bumetanide
Oral. intravenous; Tablet (1 mg).
0.01–0.02 mg/kg/dose, PO, q 6–8 h.
0.5–1 mg IV over 1–2 min, may repeat after 2–3 mins
It is 40 times more potent than furosemide.

Chlorthiazide
Oral, intravenous; Tablet (100 mg).
< 6 months: 20-40 mg/kg/d q 12h PO/IV, > 6 months: 20 mg/kg/d q 12h PO/IV.

Ethacrynic Acid
Oral, intravenous; Tablet (50 mg), injection (50 mg/vial)
0.5–1 mg/kg/dose IV q 12–24 h, 1–3 mg/kg/day q 12 h, PO.

Furosemide
Oral, intravenous; Tablet (40 mg), injection (20 mg/2 mL).
Neonates 0.5–1 mg/kg/dose q 8–24 h; maximum PO dose in newborn: 6 mg/kg/dose; maximum IV dose in newborn: 2 mg/kg/dose.
Children 0.5–2 mg/kg/dose q 6–12 h, max dose 6 mg/kg/dose
Continuous IV infusion 0.05–1 mg/kg/h.

May cause hypokalemia, alkalosis, dehydration, hyperuricemia and increased calcium excretion. Prolonged use in preterm neonates can cause nephrocalcinosis. In the presence of renal disease, it can cause ototoxicity when used with aminoglycosides.

Hydrochlorthiazide
Oral, tablet (25, 50 mg).
2–4 mg/kg/day q 12 h, PO.

Spironolactone
Oral, tablets (25, 100 mg).
2–3 mg/kg/day q 8–24 h, PO.

It is co–administered with thiazides. It is contraindicated in renal failure, hyperkalemia.

Triamterene
Oral; Tablet (50 mg triamterene + 25 mg benzthiazide).
2–4 mg/kg/day q 12 h, PO.
It is contraindicated in renal failure, hyperkalemia.

MISCELLANEOUS DRUGS

Albumin
Intravenous; Human albumin 5% (250 mL), 20% (50 mL, 100 mL).
0.5–1 g/kg/dose IV over 2–4 h.

Allopurinol
Oral; Tablet (100 mg).
10 mg/kg/day q 8 h PO.

Baclofen
Oral, intrathecal injection; Tablet (10 mg, 25 mg), injection (0.5, 2 mg/mL).

0.75–2 mg/kg/day oral q 8 h; Dosage is increased over 3 days to get the desired effect or till maximum dose achieved if needed. Max dose, < 8 years: 40 mg/day; > 8 years: 60 mg/day.

Caffeine Citrate
Oral, intravenous; Injection (20 mg/mL), oral solution (20 mg/mL) 20 mg/kg intravenous infusion as loading followed by 10 mg/kg/day oral/intravenous maintenance after 24 hours.

Calcium Gluconate
Intravenous; Injection (10% containing 100 mg/mL of calcium gluconate equivalent to elemental calcium of 8.9 mg/mL or 0.45 mEq/mL of Ca++).

Hypocalcemia 1–2 mL/kg/dose q 6 h, slow intravenous under cardiac monitoring

Maintenance 2–4 mL/kg/day q 6 h

Hyperkalemia 0.5 mL/kg over 5–10 min

Contraindication digitalized children. Extravasation can cause tissue necrosis.

Carnitine
Oral; Tablet (330, 500 mg), syrup (50 mg/5 mL), injection (500 mg/2.5 L).
50–100 mg/kg/day oral/intravenous q 8–12 h.

Deferasirox
Oral; Tablet (125, 250, 500 mg).

20 mg/kg PO per day; dose may be titrated by increasing by 5–10 mg based on serum ferritin; if serum ferritin persistently > 2500 mcg/L, may increase up to maximum of 40 mg/kg per day.

Tablet should not be chewed or swallowed whole but dispersed in apple or orange juice or in water before consumption. Preferably taken empty stomach or 30 min prior to food.

Deferiprone
Oral, capsule (250 mg, 500 mg).
50–100 mg/kg/day q 6–12 h PO.

Desferrioxamine
Intravenous, subcutaneous; Injection (500 mg).

For chronic iron overload 20–40 mg/kg/day SC over 8–12 h using battery operated pump

Acute iron poisoning IV 15 mg/kg/h OR 50 mg/kg/dose q 6 h

Contraindication anuria. May cause flushing, erythema, hypotension, tachycardia, leg cramps, fever, hearing loss and cataracts.

Dextromethorphan
Oral; Syrup (30 mg/5 mL).
1–2 mg/kg/day q 8 h.

Dicyclomine Hydrochloride
Oral; Tablet (10, 20 mg), drops, syrup (10 mg/5 mL).

Infantile colic < 6 months: 5–10 drops 15 min before feeds, 6 months–2 years: 10–20 drops 15 min before feeds, > 2 years: 1 mL every 6 hours.

Drotaverine Hydrochloride
Oral; Tablet (40 mg), syrup (20 mg/5 mL).

1–6 years 20 mg TDS
> 6 years 40 mg TDS.

Erythropoietin
Intravenous, subcutaneous; injection (2000 IU, 4000 IU)
50–100 IU/kg SC 2–3 times/week for chronic renal failure.

For anemia of prematurity 25–100 IU/kg/dose SC 3 times per week for 8–12 weeks.

Provide oral iron supplementation 2–3 mg/kg/d

Caution: Monitor for hypertension, blood urea, serum creatinine, hematocrit and clotting time. Peak effect in 2–3 weeks. Reduce dose when target attained or when hematocrit increases > 4 points in any 2 weeks period. SC route preferred to IV route.

Glucagon
Intramuscular, subcutaneous, intravenous; Injection (1 mg).
< 25 kg 0.5 mg
> 25 kg 1 mg.

Granulocyte-Colony Stimulating Factor
Intravenous, subcutaneous; Vial (300 μg).
5–10 μg/kg/day subcutaneous.

Hyoscine Butylbromide
Oral, intravenous, intramuscular; Tablet (10 mg), injection (20 mg/mL)
6–12 years 10 mg/dose q 8 h PO or 10–20 mg IV/IM bolus
Cotraindication: Glaucoma.

Lactulose
Oral; Syrup (10 g/15 mL).
1–2 mL/kg/day q 6–8 h.

Lansoprazole
Oral; Tablet (15, 30 mg)
1 mg/kg/day.

Magnesium Sulfate
Intravenous; Ampoule (50%, 4 mEq/mL of elemental magnesium).
2–3 mEq/kg/day for PEM.

For bronchodilation 100 mg/kg/dose IV.

Mannitol
Intravenous; 20% bottles (100 mL).
5 mL/kg IV over 30 min (loading dose) followed by 2 mL/kg/dose q 6 h IV for 2 days.

Metronidazole
Oral, intravenous; syrup (200 mg/5 mL), tab (200, 400 mg), vial (5 mg/mL).
Amoebiasis 30–50 mg/kg/day q 8 h for 10 days
Trichomoniasis 15 mg/kg/day q 8 h for 5 days
Anaerobic infections 20 mg/kg/day q 8 hourly for 7–10 days.

Potassium Chloride
Oral, Intravenous; Injection (1 mL = 2 mEq), syrup (20 mEq/15 mL)
1–2 mEq/kg/day q 8 h PO.

Ranitidine
Intravenous, oral; Injection (50 mg/2 mL), oral (150 mg, 300 mg).
Intravenous 1–2 mg/kg/day q 12 h
Oral 2–4 mg/kg/day q 12 h.

Sodium Bicarbonate

Intravenous; Ampoule (7.5%, 10 mL; Contains 0.9 mEq/mL).
1–2 mEq/kg/dose IV or calculate as

Base deficit × Weight × 0.6= mEq or mL of 7.5% solution of sodium bicarbonate (Total correction).

To be diluted in distilled water or 5% dextrose in a dilution of 1:6 (1 part sodium bicarbonate and 6 parts of distilled water) and given as IV infusion; Half the correction is given stat followed by the remaining in divided doses over the next 12–24 hours. Repeat blood gas as necessary. In neonates, it may be given as 1:3 dilution.

Ursodeoxycholic Acid

Oral; Tablet (150 mg, 300 mg)
10–15 mg/kg/day q 8 h.

Zinc

Oral; Syrup (10 mg/5 mL), capsules.

Diarrhea 2–6 months: 10 mg PO × 14 days

6 months–5 years 20 mg PO × 14 days

Acrodermatitis enteropathica: 6 mg/kg/day.